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Atypical Bacterial Pathogens in the Intestinal Tract

Significance of the Rokitansky-Aschoff Sinuses

Hemigastrectomy and Vagotomy for the Treatment of
Duodenal Ulcer

Experience with DPA and KIK in the Gastric Juice of
Patients with Gastric Cancer

Twenty-seventh Annual Convention

Chicago, Illinois

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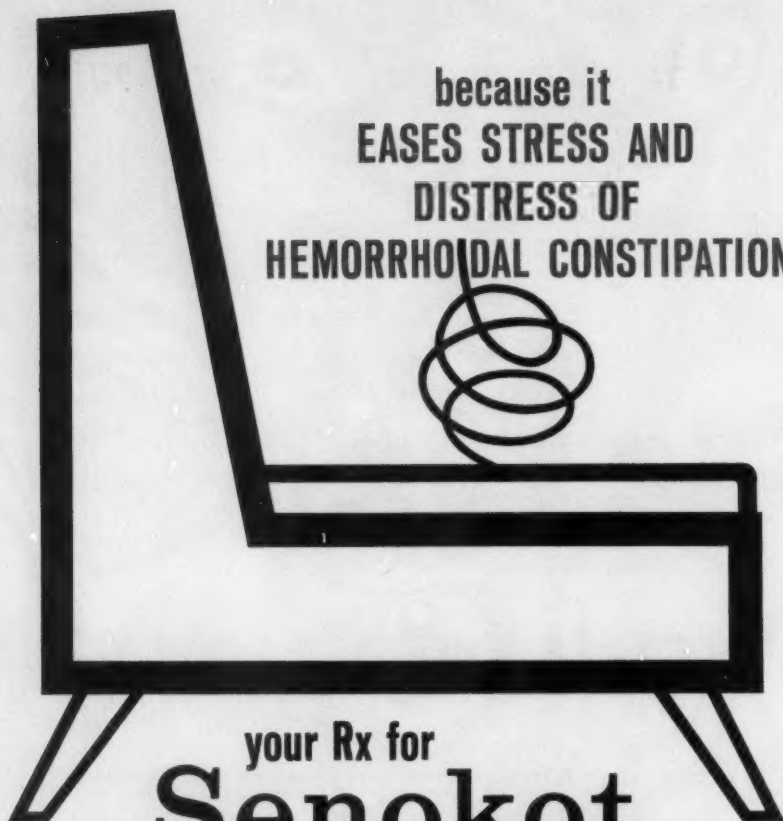
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*The Pioneer Journal of Gastroenterology, Proctology
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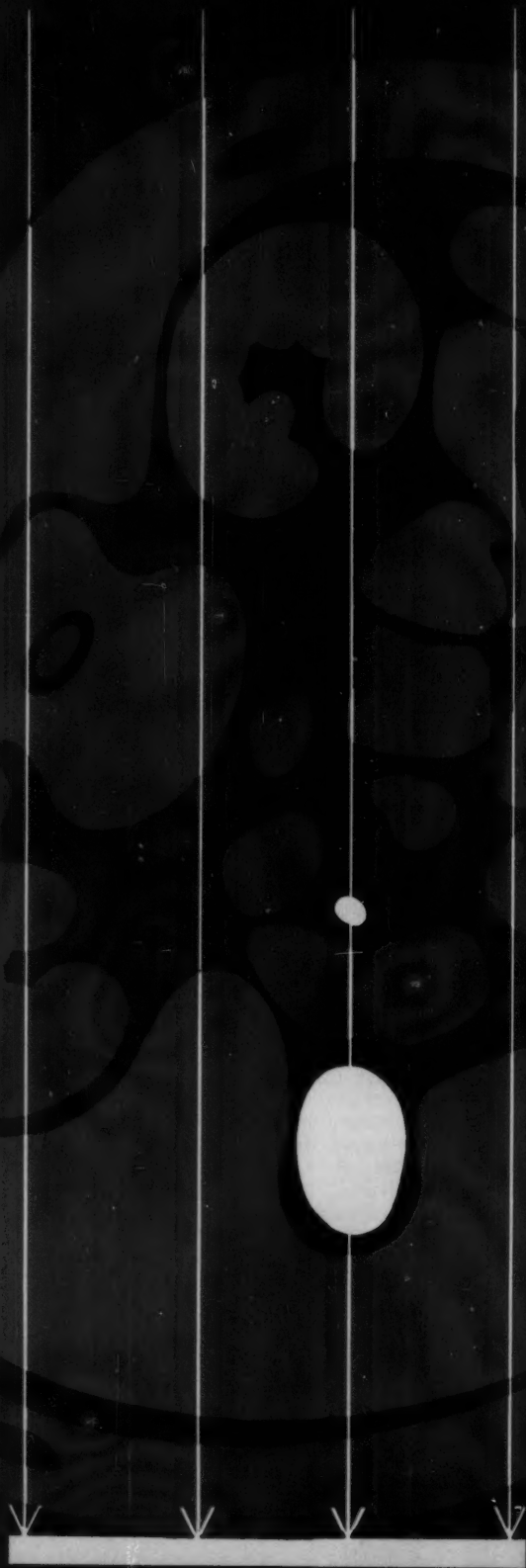
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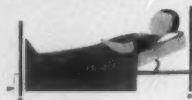
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ATYPICAL BACTERIAL PATHOGENS IN THE INTESTINAL TRACT*

WARREN C. BREIDENBACH, Ph.D., M.D.

and

ALISON MARTIN

San Francisco, Calif.

INTRODUCTION

The Salmonella and Shigella are traditionally recognized pathogens which invade the intestinal tract. Certain other bacteria, not usually regarded as pathogens, are capable of similar invasion. The latter, once established as the predominant organism in the intestinal tract, cause illness which may take one of several courses: Acute diarrhea may result; chronic diarrhea resembling amebiasis may occur. In the more severe cases there may be systemic invasion. It is the purpose of this report to describe the clinical picture which such patients present and report on bacteriological findings and treatment.

The bacteria involved have been members of the Proteus group, of the Paracolon group, *Pseudomonas aeruginosa* and subspecies of the *E. coli* group sometimes difficult to classify.

CLINICAL OBSERVATIONS

The most easily recognized clinical picture was that of chronic diarrhea not productive of blood, though mucus was often present. The duration of symptoms varied from 3-4 months to as long as 1-5 years. Endoscopic, radiological and stool examinations had demonstrated no cause for the diarrhea. In some instances previous routine stool cultures had been reported as negative by which it was meant that no Salmonella or Shigella had been isolated.

The second clinical picture was that of recurrent diarrhea such that the patient was incapacitated on 2-3 occasions per month. Ones initial diagnostic

*Read before the Western Regional Meeting of the American College of Gastroenterology, San Francisco, Calif., 5 March 1961.

From the Gastroenterology Unit, St. Joseph's Hospital, San Francisco, Calif.

impression would be that of an intermittently active regional enteritis or an amebiasis.

A third type of clinical history was that of intermittent diarrhea accompanied by abdominal distention and generalized abdominal pain of mild degree.

Of 24 patients exhibiting an abnormal stool culture there was no clue as to the origin of the infection in 14. In 8 of the 24 there was a history of recent travel in Central or South America. In 2 cases the onset of illness followed a surgical procedure which had been preceded by use of an antibiotic for the purpose of so-called bowel sterilization.

Physical examination did not reveal any specific findings.

The essential laboratory finding was a stool culture showing a pure growth or a predominate growth of a gram negative bacillus other than the usually present *E. coli*-*A. aerogenes* flora.

Treatment will be discussed subsequently.

BACTERIOLOGICAL FINDINGS

Bacteria of the intestinal tract are, for practical purposes, isolated and classified according to growth characteristics demonstrated on special media. The two commonly used media are EMB (eosin methylene blue) and SS (Salmonella Shigella) agar. Bacteria normally present in flora yield a characteristic colony growth and no further subcultures are necessary. For example *E. coli* growing on EMB media produces a dark bluish purple colony exhibiting a golden sheen. As a crude rule the pathogens produce translucent or gray colonies on EMB or SS media and so provide preliminary recognition that the organism quite probably is a "nonlactose fermenter", requiring that further identification be effected by means of subcultures. Colonies are accordingly picked and transferred to various special subculture media. Figure 1 shows in simplified form a commonly used sequence of subculture testing. The identification of a Salmonella or Shigella is not extremely difficult even though exact identification of the many subtypes, using serological methods, may be quite complex.

Most laboratories, in reporting "no enteric pathogens found" mean that no Salmonella or Shigella are present by culture. On the basis of our own laboratory experience we recommend that in cases of unexplained diarrhea the responsible physician specifically request reporting of any nonlactose fermenting organism.

If the organism isolated is a Proteus or Paracolon or other unusual enteric invader then certain points of difficulty in communication between the laboratory and the clinician can arise. Some laboratories do not report unusual organisms even when present in pure growth unless subsequent testing shows a Salmonella or Shigella. There is reluctance to imply that a particular Paracolon or Proteus or other organism is being reported, by the laboratory, as a pathogen.

It can also happen that pure growth of an unusual nonlactose fermenting organism is present and the subculture testing yields conflicting results. In other words, an organism may be a variant which is not clearly a *Paracolon* or a *Proteus*. The most confusing instances are those in which pure growth is obtained of an organism which appears to be one of the uncommonly seen members of the *E. coli* group, as for example, *E. freundii*—yet the subculture media reactions do not fit the textbook pattern.

In the present study it was not uncommon to find that our own laboratory findings, compared with those of a hospital laboratory and a government laboratory, agreed closely but not exactly as to the classification of such organ-

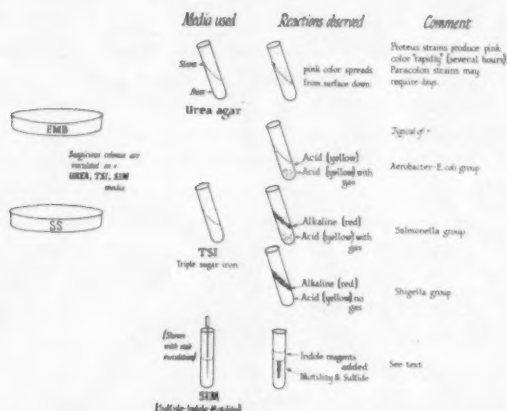


Fig. 1—Schema showing media commonly used in initial identification of enteric pathogens. TSI media demonstrates whether the organism is a "nonlactose fermenter", viz., an alkaline (red) slant. This and the reaction in butt of tube serve as a starting point in identification. SIM media further characterizes the organism: motility is shown by a hazy-cloudiness extending into the media from the stab line; sulfide production by presence of black sulfides discoloring the media; the indole reaction is positive when a purple color appears on the intersurface under special reagents overlaid onto the media. Urea media distinguishes between a rapid sweep of pink color down through the media (characteristic of the *Proteus* group), and a slow or absent color formation. The outline is crude but will suffice to allow intelligent discussion between the clinician and the laboratory in the instance of unusual organisms.

isms. The main point of agreement was that the culture had yielded a bacillus which did not ferment lactose, was not a *Salmonella* or *Shigella*, and did not belong as the dominant organism in the intestinal tract.

CASE REPORTS

Of the 24 patients with diarrhea, abdominal symptoms and an abnormal stool culture, plus an adequate clinical and bacteriological follow-up, there

were 18 who obtained remission of symptoms following antibiotic therapy. In 6 instances there was treatment failure.

We have selected 9 illustrative cases for presentation. In all cases there were negative radiological and sigmoidoscopic examinations unless otherwise noted.

Case 1:—A 65-year old white male, with duodenal ulcer, sigmoid polyps and carcinoma of the colon received antibiotic bowel preparation prior to resection. Immediately postoperatively there was diarrhea which continued over 4 months. Stool culture showed a pure growth of *Pseudomonas aeruginosa*. He was treated with kanamycin 500 mg. by mouth, q.i.d. for 7 days. The diarrhea abated, stool culture returned to normal, and though stools remained soft there had clearly been improvement.

Case 2:—After a Central America visit this 36-year old white female had acute diarrhea followed by intermittent soft stools not bothersome enough to require medical attention, but persisting for three years. The following year a hysterectomy-bilateral oophorectomy was performed and a diagnosis of endometriosis made. In the subsequent four years there was progressive and definite diarrhea. Once each month she expected and had episodes of 7-8 stools per day, such episodes lasting 4-5 days. Diarrhea was present when she was initially seen. Stool culture demonstrated *Proteus vulgaris* in pure growth. The diarrhea cleared 24-48 hours after furazolidone 100 mg. by mouth, q.i.d., was administered over 7 days. Subsequent cultures revealed normal flora. Twelve months later there had been no episodes of recurrent diarrhea.

Case 3:—After a Central America vacation this 57-year old white female had onset of watery diarrhea which occurred 3-4 times per day and had persisted for 4 weeks. Stool culture showed pure growth of a Paracolon species (reported by another laboratory as "Paracolon which does not fit any of the usual groups"). Neomycin 500 mg. q.i.d. for 10 days was administered with cessation of symptoms, return of stool culture to normal and no recurrence of symptoms with follow-up through 18 months.

Case 4:—A 56-year old white female had 4 months of diarrhea including bloody mucus. A stool culture showed normal growth. By sigmoidoscopy a polyp was found and the patient prepared preoperatively with Neomycin following which polypectomy was effected. One month later explosive diarrhea suddenly occurred with 15-20 watery stools per day. Culture showed a pure growth of abnormal colonies which were found to be Paracolon Bethesda and a *Proteus* species. Following kanamycin 500 mg. by mouth, q.i.d. the diarrhea cleared in 4 days. On the follow-up culture there were still 50 per cent of the colonies abnormal and subculture demonstrated a Paracolon of undetermined species and *Proteus morganii*. Two weeks later there was a severe recurrence of diarrhea and culture grew out a pure growth of *Proteus* of atypical type. A repeat course of kanamycin was followed, over three weeks,

by a return of the stool culture to normal, and cessation of diarrhea. Patient has been symptom-free for the subsequent 24 months.

Case 5:—A 66-year old white male was in good health until the onset of daily watery diarrhea which had been present during the month prior to being seen. Culture demonstrated a pure growth of *Aerobacter cloacae*. Barium enema showed diverticulitis of the sigmoid colon. Following 500 mg. of kanamycin q.i.d. by mouth, for 7 days the diarrhea cleared and the patient remained asymptomatic.

Case 6:—A 33-year old native of El Salvador, seven months prior to being seen, had sudden diarrhea, fever, chills and abdominal pain. Thereafter he progressively lost 15 pounds in weight, had intermittent diarrhea, and recurrent generalized abdominal pain. Stool culture demonstrated a Paracolon species exhibiting unusual subculture characteristics. It was ultimately classified as a Paracolon type 2991 (Providence type). Neomycin 500 mg., q.i.d. by mouth, for 10 days was administered. Serial stool cultures for two months thereafter showed a normal flora. A year later the patient had remained free of intermittent diarrhea and abdominal pain and the culture showed normal flora.

Case 7:—Following a vacation in Mexico this 28-year old white male had sudden onset of 10-12 watery stools per day which had persisted for two weeks despite the use of kaolin-pectate adsorbents. Stool culture showed pure growth of abnormal colonies on EMB media. Further testing did not fit the organism into any established classification; it was related to *E. freundii** and/or *E. intermedium* species. Within 24 hours after administration of 100 mg. of furazolidone by mouth, q.i.d. the diarrhea began to clear and subsequent cultures showed normal flora. He was asymptomatic for two years. Then he suffered an episode of proctitis at which time mucosal swab culture yielded a pure growth of *Proteus vulgaris*. Treatment of this has not been successful.

Case 8:—For one year this 45-year old white male had had 4-5 episodes of diarrhea per month. His wife and two children had been similarly affected; complete examination of these possible household contacts was not possible. Stool culture showed a pure growth of *Alkaliscens dispar*. Kanamycin 500 mg. q.i.d. was administered over 14 days. The stool culture returned to normal. There were no further episodes of diarrhea through a follow-up period of 5 months.

Case 9:—A 47-year old white female required, four years prior to being seen, exploratory laparotomy and small bowel resection because of bowel obstruction and infarction following previous pelvic surgery. An enterovesical fistula formed and eventually healed after long-term chemotherapy with various antibiotics, together with surgical repair. Thereafter the patient was incapacitated.

*This organism has recently been classified by some bacteriologists as a member of the Paracolon group.

tated because of 12-15 watery stools per day, with no response to a variety of postganglionic blocking agents. Stool culture demonstrated pure growth of an organism of the Paracolon group. Following administration of 500 mg. of kanamycin q.i.d. by mouth, the number of stools decreased to 4 per day. The patient regarded this (by comparison with previous years) as an improvement such that she could manage her daily housework routine. The stool cultures showed normal flora.

About 8 months later her personal physician was required to use chloramphenicol postoperatively in the treatment of a severe pyelonephritis. There was an explosive flare-up of the diarrhea with 20 stools per day again present. Stool culture demonstrated pure growth of abnormal colonies and *Proteus morganii* and *Proteus mirabilis* were found on subculture. A second course of kanamycin was administered with the culture showing a reduction in the number of abnormal colonies but *Proteus* organisms still present. Novobiocin in the amount of 250 mg. q.i.d. postoperatively was administered for 10 days. Gradually the diarrhea subsided until the patient was having 4 stools per day.

Three months later the stool culture showed normal flora and the patient had had no recurrence of the severe diarrhea.

TREATMENT

No statistical statements can be made as to results of treatment in our small series of cases. Initially we utilized neomycin or furazolidone or kanamycin. On the basis of experience, including patients now under study, we have come to prefer kanamycin as the initial drug of choice. It is not absorbed from the gastrointestinal tract. We have not observed instances of superinvasion, i.e. overgrowth of other organisms, even though cultures during the treatment period temporarily showed no growth of any organisms. In an excellent quantitative study Cohn¹ demonstrated that overgrowth by staphylococci, *Clostridia* and yeasts is not observed during administration of kanamycin.

We have not used sensitivity studies in selecting the particular antibiotic to be used. It is postulated that the primary action of the antibiotic is to suppress the growth of the invading organism until the normal flora can become re-established. Unfortunately, very little is known as to the actual biochemical changes which occur under these circumstances. We have observed during the initial several days of treatment that diarrhea and abdominal distention are often more marked than prior to treatment. Those patients who obtain good results do so 7-10 days after the 5-10 day course of therapy.

Treatment failures present a definite problem. The situation appears to be analogous to patients with pyelonephritis and a resistant and chronically lodged organism. At the present time we do not use a second course of antibiotic therapy, and cannot answer the question as to whether such patients are to be regarded as chronic "carriers".

When good results are obtained it is probably wise to advise that oral antibiotics not be used, at least for a period of several years, should the need for antibiotics arise in some other connection.

COMMENT

The main purpose of the present report is to call attention to the fact that certain bacilli, not usually regarded as of high pathogenicity, can produce abdominal symptoms and chronic diarrhea. It has long been accepted that such organisms cause acute diarrhea in children, sometimes with fatal systemic invasion. In the instance of adults there has been a gradual acceptance of such organisms as pathogens, or adaptive pathogens if the latter phrase be preferable. Such recognition has been gradual for several reasons. Firstly, systemic invasion and death does not occur as often in adults. Secondly, the bacteriologists (and quite correctly) have reiterated that simply because an organism fails to ferment lactose there is no reason to automatically classify it as a pathogen. Thirdly, it was initially believed that many of these unusual invaders were simply present by coincidence in cultures obtained during epidemics which quite possibly were epidemics caused by enteric viruses.

Enough evidence has accumulated over the years, however, to make interesting reading and make it clear that acute and (perplexing) chronic symptoms can be caused by the unusual enteric invaders to which we refer in the present article.

Morgan's report in 1906² established the organism now known as *Proteus morganii* as a species and demonstrated, including animal studies, its pathogenicity, particularly in children. Some years later, in the 1930's, the "coliform" (subsequently Paracolon) bacilli received attention, initially as curiosities and ultimately as recognized pathogens. Thus in 1943 Stuart et al³ after a comprehensive study involving more than 12,000 cultures commented: "The question of pathogenicity of coliform organisms has received considerable comment. . . . Proof is difficult to obtain because of the lack of susceptible animals. Our opinion . . . is that [the] organisms are often associated with, and under certain conditions can probably cause a mild or acute gastroenteritis. . . . Among six persons working with [these organisms] four infections resulted."

Subsequently textbooks of bacteriology⁴ classified the Paracolon bacilli into the Arizona, Bethesda-Ballerup, Providence and Hafnia groups, with the first of these definitely pathogenic and the others potentially so.

The *Proteus* group and *Pseudomonas aeruginosa* have not received the attention given to the Paracolon group but several recent publications are of interest.

Brainerd⁵ in discussing infectious diarrhea, comments on what he terms superinfection due to changes in the flora resulting from chemotherapy: "En-

terocolitis may be due to other organisms than the staphylococcus. This seems prone to occur in postoperative patients, particularly those having had gastrointestinal surgery. It can be due to a variety of organisms. We have noticed it is often due to *Pseudomonas aeruginosa*, so-called *B. pyocanea*. Apparently certain species of *Proteus* can do likewise."

Forkner in a recent monograph⁶ has documented a clinical picture resembling typhoid fever but caused by *Pseudomonas aeruginosa* enteritis.

Finally, there is no doubt that the enterobacteria as a group now account for an increasing number of invasive infections. Finland⁷ has reported that in 1935 the enterobacteria accounted for 11.7 per cent of pneumonia cases with bacteremia; by 1957 there had been an increase to 34.5 per cent. The respective figures for fatal cases showed a rise from 9.0 to 47.7 per cent.

Putting all of this together we conclude that the unusual enteric invader is worth recognizing as a clinical entity. As to terminology we prefer, from the Standard Nomenclature of Disease: enterocolitis due to (..... name of organism) 604-130, which refers to "organisms of rare pathogenicity".

SUMMARY

We have studied and reported upon patients with intermittent or chronic diarrhea caused by enteric bacilli not usually pathogenic. These include the Paracolon group, the *Proteus* group, *Pseudomonas aeruginosa*, and unusual variants which are difficult to classify by the usual taxonomy.

The case reports illustrate the types of clinical problems met and the responses which can be obtained after antibiotic therapy.

A brief review of bacteriology is provided; the practicalities of liaison between clinician and laboratory are stressed.

The literature in perspective is reviewed.

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LEFT-SIDED COLONIC LESIONS MASQUERADING AS ACUTE APPENDICITIS*

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There are a persistent small group of patients who initially present the classical signs and symptoms of either acute or subacute appendicitis, but whose etiological factors arise from unsuspected obstructing neoplasia (usually) of the left descending colon. To fail to recognize such an instance may constitute a grave tragedy for that particular patient because the optimum time for surgical excision of the neoplasia before distant metastases occurs may be irretrievably lost. As a consequence, that individual is doomed to an early and unnecessary needless death.

Embryologically, the right half of the colon arises from the midgut and is chiefly concerned with the absorption of the fluid contents within the proximal colon. This segment of the colon is thin-walled and has little well developed muscularis within its walls. In contrast, the left half of the colon is derived from the hind-gut and is thick-walled, of smaller caliber, and possesses a strong and powerful muscularis. It is chiefly concerned with the propulsion of the feces further caudad for ultimate disposal by defecation.

It has long been known that the human vermiform appendix is notoriously vulnerable to rapidly acute gangrenous appendicitis whenever its lumen becomes plugged by nonabsorbable intraluminal contents. The blood and lymphatic supply to the process vermicularis is of an end vessel configuration with no collateral circulation, except at its basilar juncture with the cecum for a distance of one centimeter. Thus, if any inflammatory process damages either the blood or lymphatic supply to the human appendix, a fulminating, acute, gangrenous appendicitis is the usual result.

Therefore any obstructing lesion in the left half of the colon can initiate powerful reverse peristalsis and force undigested foreign intraluminal material into the appendiceal lumen, and thus set up a "blind-loop" acute inflammatory process. It is wiser therefore, when operating upon an individual over the age of 40 years, to keep these facts in mind and not be caught "napping" with an unrecognized obstructing left colonic lesion on your hands.

Over five years ago I summarized¹ my then 31 consecutive years of studying 50,000 specimens of the human vermiform appendix. Since then, an additional 11,118 examples have been added to this large group of study data.

Tables I and II are self-explanatory. They tabulate and summarize this large amount of material for the convenience of the reader.

*Read before the Western Regional Meeting of the American College of Gastroenterology, San Francisco, Calif., 5 March 1961.

It was found that 16.66 per cent of this large total number of specimens were obtained from individuals over the age of 40 years. If we subtract the 1,291 postmortem appendices from consideration, we have left 8,890 (14.54 per cent) surgical specimens to study in these older individuals.

In the entire 10,181 specimens derived from various sources, 317 (3.08 per cent) presented various obstructing lesions in the distal left colon. Of these lesions 82.3 per cent were carcinomas. Diverticulitis caused an additional 9.46 per cent of obstructions leading to appendicitis. Volvulus and sarcomas equally produced 3.79 per cent apiece of appendicitis. Miscellaneous lesions added a final 0.63 per cent incidence of inflammatory lesions of the appendix.

TABLE I
SOURCE OF MATERIAL

Source	Whole series		Patients over age of 40 years	
	Number	Per cent of 61,118	Number	Per cent of 10,181
I. Surgical <i>Type of lesion</i>				
Perforative or gangrenous	5,634	9.2	1,060	10.3
Simple acute	8,234	13.4	1,211	11.8
Subacute	8,004	13.0	1,302	12.7
Chronic	20,369	33.6	4,183	40.7
Prophylactic appendectomy	12,223	20.0	1,054	10.3
Miscellaneous lesions	1,992	3.2	80	0.8
II. Postmortem (Various 4,134 82.68% stated to be "Not Remarkable".)	4,665	7.6	1,291	12.6
Totals	61,118	100.0	10,181	99.2

In this study, benign colonic polyps and intermural leiomyomata were excluded from consideration. The average time lost from the date of the appendectomy to when it became clinically apparent that there was a left colonic obstruction present averaged 4.6 months. Seventy-eight per cent of these obstructing colonic lesions, when finally recognized and surgically explored, dismally revealed that the lesions by that time had widely spread beyond the local confines of the left colon. Exploration revealed gross evidence of distant metastases. The five-year survival-rate for these 86.2 per cent neoplasias was a discouraging 8.44 per cent.

From this very brief presentation it is quite obvious that we must remember that an obstructing lesion of the left colon, in those individuals past 40 years of age is capable of producing acute appendicitis and masquerading as that disease until it is too late to excise the tumor while it is still localized and

TABLE II
TYPES OF LEFT COLONIC LESIONS PRODUCING APPENDICITIS
IN PATIENTS OVER 40 YEARS OF AGE

Source	10,181 cases		Unsuspected left colonic lesion	
	Number	Per cent	Number	Type of lesion and #
Perforative and gangrenous	1,060	10.3	84	70—Carcinoma 2—Sarcoma 10—Diverticulitis 2—Volvulus
Simple, acute	1,211	11.8	79	69—Carcinoma 6—Diverticulitis 4—Volvulus
Subacute	1,302	12.7	97	81—Carcinoma 7—Sarcoma 8—Diverticulitis 1—Volvulus
Chronic	4,183	40.7	41	32—Carcinoma 2—Sarcoma 3—Diverticulitis 4—Volvulus
Prophylactic appendectomy	1,054	10.3	12	6—Carcinoma 3—Sarcoma 2—Diverticulitis 1—Volvulus
Miscellaneous lesions	80	0.8	1	1—Carcinoma
Postmortem	1,291	12.6	3	2—Carcinoma 1—Diverticulitis
Totals	10,181	99.2	317	261—Cases, 82.33% 30—Div., 9.46 12—Vol., 3.79 12—Sar., 3.79 2—M.L., 0.63
(Note:—317 is 3.08% of 10,181)			317	100.00

resectable. It appears from this study that possibly three per cent of patients past the age of 40 years, suffering with acute appendicitis, will also possess an obstructing distal left colonic neoplasia. In most circumstances, a quick and gentle exploration of the left colon, before performing an appendectomy, will

carry little increase in operative risk to the patient. Such a brief maneuver may save your patient's life and save the surgeon from tremendous embarrassment in the future.

CONCLUSIONS

1. Since 1924, 61,118 specimens of the human vermiform appendix have been continuously studied.

2. From this data it appears that about three per cent of patients over the age of 40 years and suffering from appendicitis will have an unrecognized accompanying and etiological-causing obstructing lesion (Eighty-six per cent chance of being malignant) of the left descending colon.

3. A plea is made for surgeons to carefully file this fact in their memory for possible future use, thereby preventing great embarrassment to themselves, but of far more importance—the prevention of procrastination and loss of present opportunity to perform a curative resection before the onset of distant metastases.

4. Finally, remember that a left-sided colonic lesion advanced enough to cause lumen obstruction, has already been in unrecognized existence entirely too long for the normal longevity of that particular patient.

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SOME PROBLEMS OF INTESTINAL ABSORPTION*

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Considering the critical importance of intestinal absorption in an organism's economy, the current heightened interest in this subject is to be welcomed. Electron microscopy, histochemical and enzyme studies, as well as some of the technics used for the investigation of transport mechanisms in the cells of other tissues, are yielding much information about a neglected organ. On the clinical front too, new technics are leading to an orderly scheme of differential diagnosis and are contributing to our knowledge of the pathogenesis of some of the diseases causing faulty absorption. By presenting a sampling of some clinical problems in absorption seen in the past year and a half at

TABLE I
DIFFERENTIATING TESTS IN MALABSORPTION

Test	Pancreatic Origin	Intestinal Origin
I ¹³¹ triolein	Abnormal	Abnormal
I ¹³¹ oleic acid	Normal	Abnormal
Co ⁶⁰ Vitamin B ₁₂	Normal	Abnormal
d-xylose	Normal	Abnormal
Glucose tolerance	Diabetic	Flat
Osteomalacia	Absent	Often present
Secretin	Abnormal	Normal
Gastrointestinal series	Pancreatic calcium	"Deficiency" pattern
Jejunal biopsy	Normal	Abnormal

Stanford, I hope to illustrate how some of the current technics can be employed in diagnosis and thereby, at least in some instances, permit rational therapy.

Before launching into the diagnostic study of a patient with malabsorption, one must recognize that the malabsorption exists. When a semistarved patient appears with a sore tongue and a bloated abdomen complaining of fatty diarrhea, malabsorption is self-evident. But not all patients have frequent or loose stools; the weight may be stable though low; and one should be aware that some patients have unexplained anemia, bone pain and fractures, tetany

*Read before the Western Regional Meeting of the American College of Gastroenterology, San Francisco, Calif., 5 March 1961.

or bleeding, which overshadow other more typical symptoms. Once suspected, malabsorption must be confirmed, which generally means establishing the presence of steatorrhea. The most reliable way of doing this, if not the most tidy, is to measure the fecal excretion of fat; this determination remains the standard by which other tests are evaluated. The next step is to distinguish maldigestion, most often pancreatogenous, from intestinal failure. Table I demonstrates how this may be done utilizing a number of differentiating tests. Because none of these tests is infallible, it is wise to use several of them to pinpoint the defect. Pancreatic insufficiency is presumed to be present if the radioiodinated fatty acid, oleic acid, is absorbed normally, but triglycerides are not¹. Evidence of diabetes, pancreatic calcification and a decreased concentration of bicarbonate in the duodenal aspirate after secretin stimulation clinch the diagnosis.

In contrast, neither fatty acids or triglycerides are normally absorbed in idiopathic sprue or other types of intestinal mucosal failure. Evidence of mul-



Fig. 1

Fig. 1—Normal peroral jejunal biopsy.

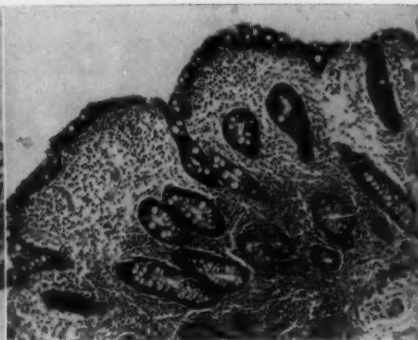


Fig. 2

Fig. 2—Biopsy showing villous atrophy of idiopathic sprue (Case 1).

tle absorptive defects may be found when Vitamin B₁₂, calcium and Vitamin D, and d-xylose absorption are tested. Peroral suction biopsy of the intestinal mucosa may reveal any of a number of characteristic abnormalities. Where specific therapy is available, the clinical response may lend support to the diagnosis; for example, replacement of pancreatic enzymes in pancreatic insufficiency, a gluten-free diet in sprue, and antibiotics if bacterial overgrowth interferes with absorption. In the cases that follow, pancreatic insufficiency could be excluded so that one was confronted with determining the reason intestinal absorption *per se* had failed.

Case 1:—A 51-year old white male had diarrhea, abdominal cramps, anemia and weight loss beginning in 1942. With a substantial intake of calories during the next 17 years, he suffered only from mild diarrhea and was able to maintain

his weight at some 20 pounds below his ideal weight. In the year prior to admission to our hospital, however, he passed five light-colored, frothy malodorous stools daily; he was bothered by flatulence, leg cramps and edema. Vitamin B₁₂, folic acid, pancreatic substance and bile hadn't helped him. Examination revealed a blood pressure of 100/60, marked thinness, a distended abdomen and slight peripheral edema.

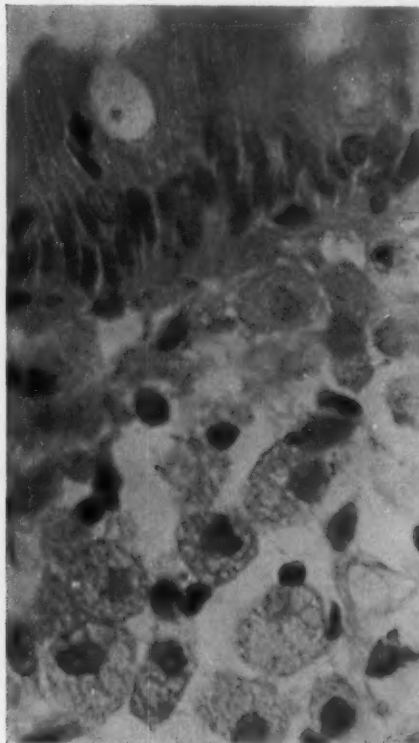


Fig. 3

Fig. 3—Large vacuolated macrophages in *lamina propria* of jejunum from Case 2.

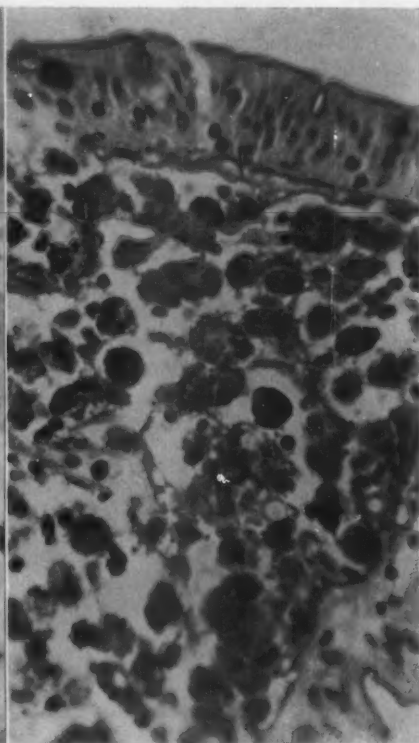


Fig. 4

Fig. 4—PAS-positive material in macrophages in *lamina propria*; typical of Whipple's disease (Case 2).

Films of the small bowel showed dilatation and clumping of barium. These findings, though not specific, are often seen in sprue. Therefore, a suction biopsy of the jejunum was obtained with the instrument devised by Rubin and associates². The broad, stunted villi, the inflammatory cell infiltrate and the ragged flattened villous surface epithelium seen in Figure 2 are in sharp contrast to the histology of the normal jejunum seen in Figure 1. The abnormal mucosal

pattern and evidence of fat malabsorption allowed a diagnosis of idiopathic sprue to be made. Consequently, a gluten-free diet (prohibition of foods containing wheat, rye, oats and barley) was begun. Before therapy, oleic acid labeled with I^{131} was found in the blood in a maximum amount of 5 per cent of the ingested dose of radioactivity. (The normal value in our laboratory is at least 9 per cent at the 2-, 4- or 6-hour sampling.) After four months of therapy, during which time there was a 20 pound weight gain and a return to normal defecation and strength, the oleic acid absorption increased to 7.6 per cent. The definite but incomplete response was reflected by the 24-hour fecal fat excretion



Fig. 5—Mucosal inflammation of distal jejunum (Case 3).

of 6 gm., slightly above normal. Although there was no anemia, hypoproteinemias or hypoprothrombinemia, deficient calcium absorption was implicated by a serum calcium value of 8.4 gm. per cent; the serum phosphorus was 3.2 mg. per cent, and the alkaline phosphatase 3.4 Bessey-Lowry units (normal 0.8-2.3). Treatment with a gluten-free diet and supplements of Vitamin D raised the calcium to normal, 9.5 gm. per cent, and lowered the alkaline phosphatase to 1.3 units. Although there was chemical evidence of osteomalacia, bone demineralization was not seen radiologically.

Case 2:—A 51-year old slot-machine repairer was admitted in March 1960 because of severe diarrhea and weight loss of 40 pounds of four months' duration. The diarrhea began after several days treatment with a broad-spectrum antibiotic; later, monilia were recovered from the feces. Despite treatment with mycostatin, the patient persisted in passing up to 25 watery stools daily. Of importance was a 30-year history of migratory polyarthritis affecting the wrists, knees, ankles and low back; each episode lasted not more than 3 days and left no residual deformity. He was a thin man with increased skin pigmentation and easily palpable cervical and axillary lymph nodes. The only abdominal abnormalities were hyperperistalsis and slight distention. The joints were normal; but during his hospital stay, an attack of ankle pain and swelling was observed.

TABLE II
RESPONSE TO THERAPY IN CASE 3 USING THE SCHILLING TEST

Treatment	Duration (days)	Symptoms	% excretion Co ⁶⁰ Vitamin B ₁₂ *
Gluten-free diet	45	Severe	1.3
Prednisone 25-20 mg.	15	None	14
Prednisone 15-10 mg.	30	Mod. severe	3.3
Neomycin 3 gm.	9	Mod. severe	4.4
Prednisone 25-17.5 mg.	69	None	8.0

*Per cent of administered radioactivity excreted in urine in 24 hours. Normal 9 per cent or more.

Examinations of the blood and urine were normal, but the stool contained excessive fat. Both the I¹³¹ triolein and oleic acid absorption tests were abnormal, which implied an intestinal mucosal block. Electrophoresis of the serum revealed increased alpha and beta globulins, normal gamma globulin and decreased albumin; the total protein was 5.5 gm. per cent. No pathogenic organisms were found in the stool. X-ray study of the small bowel showed generalized dilatation and obliteration of the mucosal pattern in the jejunum and ileum.

A suction biopsy of the jejunum (Fig. 3) showed a fairly normal villous pattern but the *lamina propria* was packed with large cells having a vacuolated appearance. Periodic acid-Schiff staining demonstrated that the material distending these mucosal macrophages was PAS positive (Fig. 4), suggesting a mucoprotein composition. This histological picture is pathognomonic of Whipple's disease—also misnamed intestinal lipodystrophy—a systemic disorder charac-

terized by a clinical pattern of arthritis, lymphadenopathy, polyserositis and diarrhea. The macrophages containing mucoprotein inclusions may be found in peripheral and mesenteric lymph nodes, in intestinal mucosa, as well as in other tissues, including the brain. The accumulations of PAS-positive macrophages in the mucosa block entry of nutrients from the gut lumen; the origin of the cytoplasmic inclusions is unknown. Although jejunal biopsy led to a definitive diagnosis in this case, high-dose corticosteroid and corticotropin treatment did not alter the malabsorption or prevent a fatal outcome. Reports of success



Fig. 6—Radiological demonstration of multiple large diverticula of duodenum and jejunum in Case 4.

with antibiotics³ appear encouraging, but it might be remembered that an antibiotic seemed to initiate the diarrhea in the present case.

Regional enteritis can result in malabsorption, especially after surgical resection of a segment of ileum or if severe mucosal involvement is present.

Case 3:—Here malabsorption was diagnosed prior to the detection of the intestinal inflammatory process and continues to dominate the clinical course. The patient, a 26-year old physician, was first seen in June 1960 because of two months of diarrhea. Actually, it had been only in the preceding two weeks that

loose stools, five per day, had been a problem. He had lost 5 pounds and had some malaise. Examination was negative except for a slightly enlarged liver. Blood, stool and thyroid studies did not reveal abnormalities; sigmoidoscopy was negative and x-ray examinations of the entire alimentary tract were interpreted as normal. He began to display a low grade fever in the evening associated with fatigue and some generalized abdominal cramping, which preceded the passage of from six to ten watery movements in the subsequent weeks. Continued weight loss led to the suspicion that malabsorption was involved; the suspicion was confirmed by the finding of a fecal fat excretion of 14 gm. per 24 hours, a value three times normal. Faulty absorption of both radioiodinated triolein and oleic acid pointed to an intestinal rather than a digestive defect. Failure to absorb radiocobalt-labeled Vitamin B₁₂ (Schilling test) even with added intrinsic factor supported this contention. A proximal jejunal biopsy, however, was normal; nevertheless, a gluten-free diet was prescribed

TABLE III
RESULTS OF SCHILLING TESTS IN CASE 4

Date	Administered	% excretion Co ⁶⁰ Vitamin B ₁₂
10/6/59	Co ⁶⁰ Vitamin B ₁₂	0
10/8	Co ⁶⁰ Vitamin B ₁₂ + intrinsic factor	0.5
10/13	Co ⁶⁰ Vitamin B ₁₂ + chlortetracycline 2 gm. x 4 days	9.4
10/14	Co ⁶⁰ Vitamin B ₁₂ + chlortetracycline 2 gm. x 5 days	21

because of the possibility that the patient had idiopathic sprue but that, for some reason, the involved bowel had been missed. After six weeks of dietary and symptomatic therapy, there was no clinical improvement and prednisone, 25 mg. per day, was begun. Within one week the diarrhea and malaise had diminished; within 3 weeks the patient felt well and was regaining the 20 pounds he had lost. Reduction of the prednisone dose below 15 mg./day, however, caused a relapse. At this point, an attempt (with the assistance of Dr. Lloyd Brandborg) was made to biopsy the ileum, which, on a second small bowel x-ray, showed thickened and irregular mucosal folds and some dilatation. Although the biopsy capsule did not reach the ileum, a specimen was obtained from the distal jejunum. When examined microscopically (Fig. 5), the mucosa was found to be heavily infiltrated with plasma cells and lymphocytes, and there were scattered eosinophils; the villi were well-preserved. A diagnosis of nonspecific enteritis was made, which together with the x-ray findings suggested that the patient was suffering from Crohn's disease, with the predominant manifestation being malabsorption. Table II demonstrates the value of the

Schilling test in obtaining an objective measurement of the response to therapy. The trial of neomycin was undertaken to exclude the possibility that intestinal bacteria were preventing normal absorption. When this maneuver failed, prednisone, 25 mg./day, was reinstituted, and was again successful.

Case 4:—The problem of colon bacteria in the small intestine interfering with normal absorption as occurs in the "blind loop" syndrome is illustrated. For 5 years this 85-year old man (whose case will be published in detail by Crawford and Freeman⁴) had intermittent abdominal distress and diarrhea. Corticosteroids were somewhat helpful during that time. Intractable diarrhea, however, marked weight loss and moderate anemia led to our investigations in 1959. He was emaciated and had slight mucosal atrophy of the tongue. Purpura were found in the skin of the upper extremities; vibratory and position sensation in the legs were decreased. Examination of the blood revealed: hemoglobin, 10.3 gm. per cent; hematocrit, 31 per cent; red blood cells, 3,100,000; reticulocytes, 0.9 per cent; platelets, 148,000. (The hemoglobin had ranged from 13 to 14 gm. per cent on several occasions during the period 1955-57. Gastric secretion of hydrochloric acid had been demonstrated in 1957.) The bone marrow was megaloblastic. No appreciable $\text{Co}^{60}\text{B}_{12}$ was excreted with or without the addition of intrinsic factor; reticulocytosis was present after Vitamin B_{12} injection. Not only was there failure to absorb Vitamin B_{12} but fats were not absorbed normally either, as evidenced by a maximum blood I^{131} triolein value of 6 per cent. A barium meal gave the clue to the reason for malabsorption (Fig. 6): numerous, large diverticula of the duodenum and jejunum were present. Jejunal diverticula by permitting stasis of intestinal contents and proliferation of bacterial flora can result in megaloblastic anemia and steatorrhea⁵. Treatment with broad-spectrum antibiotics or surgical resection of the affected bowel reverses the malabsorption. Serial Schilling tests with the addition of intrinsic factor and antibiotics (Table III) establish this diagnosis, and generally exclude pernicious anemia. Continued treatment with chlortetracycline controlled the diarrhea; the hemoglobin level rose until the patient unexpectedly died in his sleep. Autopsy showed 30 small intestinal diverticula and a normal gastric mucosa.

SUMMARY AND CONCLUSIONS

The four cases discussed give some idea of the variety of conditions that can lead to intestinal malabsorption. Our understanding of pathogenesis in these conditions is limited. For example, we don't know why absorption is impaired in idiopathic sprue nor do we know what the role of gluten is. The source of the abnormal mucoprotein in Whipple's disease and the cause of regional enteritis are likewise enigmas. The relation between intestinal bacteria and absorption is puzzling. Nevertheless, new technics which enhance our diagnostic acumen and fundamental discoveries in the laboratory are throwing new light on these and other problems of intestinal absorption.

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SIGNIFICANCE OF THE ROKITANSKY-ASCHOFF SINUSES*

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In the gallbladder wall are several different epithelial structures, some of them communicating with the lumen of the viscus, others not. They have often been mistaken for one another. The purpose of this paper is to clarify the identities of these structures and to elaborate on the nature of one of them, namely the Rokitsky-Aschoff sinuses.

Mucus-secreting acinar structures like those which occur along the extra-hepatic biliary ducts are frequently noted also at and near the neck of the gallbladder. Some of these penetrate the muscular coat of the viscus just as Brunner's glands extend through the *muscularis mucosae* into the submucosa of the duodenum¹. Similar acini lined by secreting cuboidal cells occur also occasionally over the mucosal surface of the body of the gallbladder. These acini are usually level with or protrude into the lumen of the viscus. When they are wide spread and appear over most of the mucosal surface the condition should be called *cholecystitis glandularis*.

In cholesterolosis of the gallbladder lipid-laden large mononuclear cells appear in abundance within the *lamina propria* and the folds become broader. Papillary projections appear in focal areas. A number of these projections become encrusted, later are detached and drop into the lumen to form the centers of mulberry-shaped mixed gallstones.

Heterotopic structures such as pancreatic tissue and gastric and intestinal epithelium are occasionally encountered in the wall of the gallbladder². They can be identified by their particular pattern and cellular components.

The fundus is the usual site of adenomyoma of the gallbladder. The epithelial component of the adenomyoma forms spaces lined by cuboidal or columnar cells. These spaces usually communicate with the lumen of the viscus. They are in an abundant fibromuscular stroma with the smooth muscle cells in a streamlike pattern. These adenomyomas of the gallbladder are malformations, hamartomas, rather than neoplasms. They probably represent the anlage either of a part of the fundus that did not develop or of the fundus of an undeveloped bifid or bilobed gallbladder³.

In the outer layer of the gallbladder wall aberrant bile ducts are encountered. These are observed more often on the surface of the viscus attached to the liver than on the surface covered by peritoneum. They do not communicate

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with the lumen of the viscus, but may do so with intrahepatic biliary ducts. These aberrant bile ducts were first observed by Luschka in 1863. The Luschka

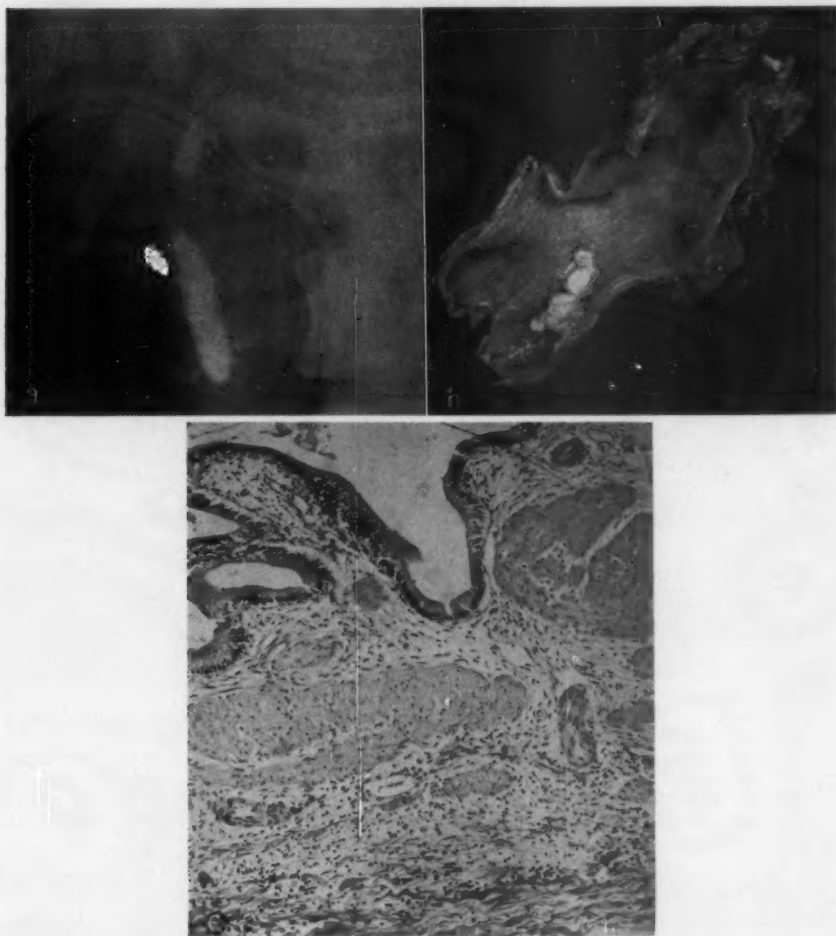


Fig. 1—Roentgenographic a. gross b. and microscopic c. appearances of a gallbladder removed surgically from a 28-year old man with intermittent pain in the epigastrium for three months and continuous pain for three days. The Rokitansky-Aschoff sinuses are visualized roentgenographically (courtesy of Dr. Harry L. Barton). The gallbladder contained a paste of calcium carbonate. Microscopically there are hypertrophy of the muscular coat and outpouchings of the mucosa between muscle bundles. One of these is adjacent to a penetrating blood vessel, x 100.

ducts are embryonic remnants having the structure and appearance of an intrahepatic biliary duct.

In the wall of the normal human gallbladder of embryos, of fetuses, of newborns, of children and of adults, no outpouchings of the gallbladder mucosa penetrate the muscular coat. When, however, there is an increase in thickness of the muscular coat of the gallbladder, outpouchings are constantly present in abundance and they penetrate the muscular coat to varying depths. These outpouchings occur where blood vessels penetrate and weaken the muscular coat. Such outpouchings of the mucosa were first recorded by Rokitansky in 1842, and were described microscopically by Aschoff in 1905, and subsequently named Rokitansky-Aschoff sinuses by Halpert in 1926⁴. Further progress was made in the knowledge of the Rokitansky-Aschoff sinuses in 1948, when March⁵ of Philadelphia visualized them during cholecystography. A study in 1960 by

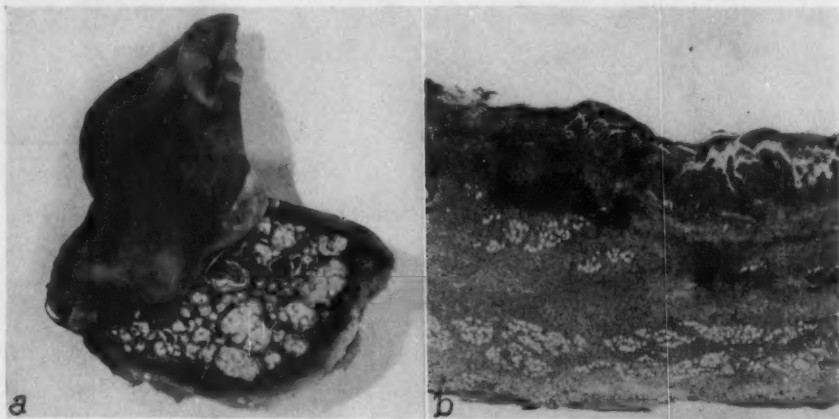


Fig. 2—Gross a. and microscopic b. appearances of a gallbladder removed from a 72-year old man who had right upper quadrant pain for three days. The acutely inflamed gallbladder contains numerous conglomerate gallstones that appear to have a delicate white shell of calcium carbonate. The microscopic appearance indicates that the acute cholecystitis is grafted on a chronic cholecystitis evidenced by hypertrophy of the muscular coat, the presence of outpouchings of the mucosa—the Rokitansky-Aschoff sinuses—and the broadening of the perimuscular layer, x 10.

Elfving⁶ of Helsinki reaffirmed the detailed morphologic observations made by Halpert in 1927⁷. The Rokitansky-Aschoff sinuses are the most important of the epithelial structures occurring in the wall of the gallbladder. They are of diagnostic significance, playing an important role in chronic cholecystitis with cholelithiasis and more particularly in chronic cholecystitis with superimposed acute cholecystitis.

Knowledge of the manner in which the outpouchings form is the key to the understanding of their role in chronic cholecystitis. Morphologic and experimental data indicate that the function of the muscular coat of the gallbladder is to adjust to the change in content of the vesicle⁸. The inner layer of the

muscular coat is composed of longitudinal or oblique muscle bundles that are separated from the lining epithelium by a delicate *lamina propria*. Frequent or continuous overdistention of the viscus leads to ironing out of the folds of the mucosa and the increased intravesicular tension induces hypertrophy of the muscular coat. When such a gallbladder contracts the mucosa is crowded and forced to dip between the muscle bundles and to form mucosal outpouchings—the Rokitansky-Aschoff sinuses. The most favorable sites for such outpouchings are adjacent to penetrating blood vessels.

Hypertrophy of the muscular coat, the presence of Rokitansky-Aschoff sinuses and the broadening of the perimuscular layer together with infiltrations

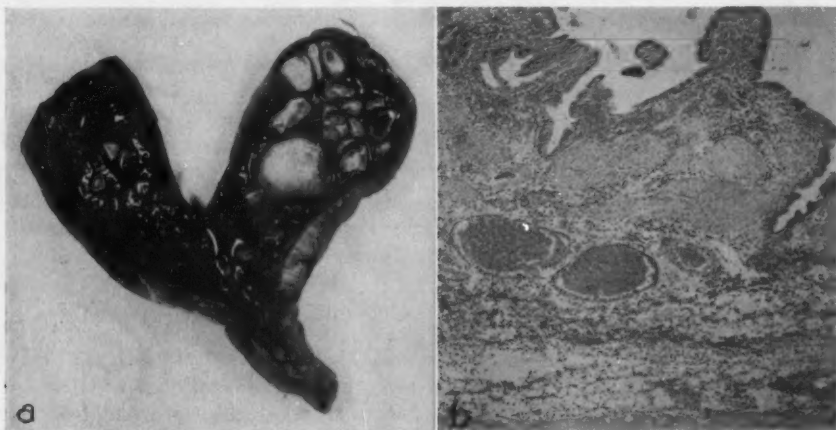


Fig. 3—Cross, a. and microscopic b. appearances of a gallbladder surgically removed from a 53-year old man who had a sudden onset of severe epigastric pain, nausea and vomiting for 24 hours. The acutely inflamed gallbladder contains faceted mixed gallstones of varying sizes and a large combined gallstone. Microscopically there is hypertrophy of the muscular coat with outpouchings of the mucosa extending through the muscular coat. Superimposed is the acute process with conspicuous edema of the wall and extravasations of erythrocytes, $\times 100$.

of lymphocytes, plasma cells, and large mononuclear cells are the standard criteria for the microscopic diagnosis of chronic cholecystitis. The concomitant presence in such gallbladders of space-occupying calculi suggests an intimate relationship between chronic cholecystitis and cholelithiasis. This association is constant when the calculi are of the mixed or combined variety. On the other hand, pure gallstones may be present in the viscus in the absence of microscopic change in the gallbladder. Their continued presence, however, eventually leads to chronic cholecystitis. Chronic cholecystitis may also be induced by intermittent or continuous abnormal composition of the bile. Furthermore, attenuated or usually nonpathogenic enteric organisms may cause the chronic inflammatory

reaction. These variables alone or in combination operate in producing chronic inflammation of the gallbladder. Whatever the principal inducing cause may be, certain features of chronic cholecystitis are characteristic. The most important of these is the almost constant presence of gallstones in the chronically inflamed gallbladder. Pure or mulberry-shaped mixed gallstones are a cause of chronic cholecystitis. The other mixed gallstones and the combined gallstones are the sequel to the chronic inflammatory state of the viscus. Familiarity with the chemical composition and structure of the gallstones aids therefore in interpreting their role in the inflammatory process. Pure gallstones are hepatogenous, that is, their formation is associated with an increase in the hepatic bile of one of the stone-forming components. Mixed gallstones on the other hand are cystogenous. They form in the gallbladder when the resorptive function of the viscus is impaired so that the solvents are reabsorbed faster than the stone-forming constituents.

Chronic cholecystitis usually produces vague right upper abdominal distress and distaste for fatty foods. Occasionally the calculous content of the viscus may be felt by bi-manual palpation. Usually the gallstones may be visualized and occasionally the Rokitansky-Aschoff sinuses verified roentgenographically (Fig. 1). The presence of biliary calculi within the viscus lends clinical importance to chronic cholecystitis. The gallstones may pass through the dilated cystic duct and obstruct the common bile duct producing jaundice. The most important feature of chronic cholecystitis with cholelithiasis is, however, that it predisposes to the development of acute cholecystitis.

Acute cholecystitis, from whatever cause, in a previously intact gallbladder is a nonspecific inflammation. Such an acute process is usually progressive and may end in perforation of the gallbladder with focal abscess or diffuse peritonitis. In only rare instances does such an inflammation subside; thus, acute cholecystitis does not subside into chronic cholecystitis. Gallbladders surgically removed for acute cholecystitis that contain gallstones, pure, mixed, or combined, are in fact gallbladders with the acute cholecystitis grafted on a chronic cholecystitis (Figs. 2 and 3). Grossly, such a gallbladder differs little from one with acute cholecystitis except for the presence of calculi within the viscus. Microscopically, however, the criteria of the chronic inflammatory process are easily ascertained. There are outpouchings of the mucosa through the hypertrophied muscular coat comprising the Rokitansky-Aschoff sinuses, and there is increase of the connective tissue particularly in the perimuscular layer. There are varying degrees of infiltration with lymphocytes, plasma cells, large mononuclear cells and some eosinophilic granulocytes. Superimposed on the chronic process is an acute inflammatory reaction. A hemorrhagic fibrinopurulent exudate covers the denuded or ulcerated areas of the mucosa. All the layers are markedly spread apart by inflammatory edema and are infiltrated with freshly extravasated erythrocytes and neutrophilic granulocytes, and the serosal surface of the gallbladder is covered by fibrin.

SUMMARY

Of the several epithelial structures in the gallbladder wall, only the Rokitansky-Aschoff sinuses have diagnostic significance. They are always associated with hypertrophy of the muscular coat and with the presence of biliary calculi. They may occasionally be visualized by roentgenographic methods. Their presence is the principal criterion by which chronic cholecystitis is diagnosed microscopically and by which acute cholecystitis superimposed upon chronic cholecystitis is microscopically identified.

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GASTROSCOPY*

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The development of the flexible gastroscope in 1932¹ paved the way for the complete study of the gross morphology of the interior of the stomach. In the intervening years, the widespread use of gastroscopy, combined with gastrointestinal x-ray evaluation and microscopic study of gastric biopsy specimens, has served to demonstrate its value as well as its limitations. Gastroscopic examination has stood the test of time, and although some have become disenchanted with the method, it is perhaps not too unfair to say that they are largely among the ranks of those who expected too much, or who practiced it too little. The gross inspection of any mucosal surface frequently leaves much to be desired. An attempt to interpret too minutely may lead to errors, although certainly the view of the living gastric mucosa is far superior, from a diagnostic standpoint, than that of the resected specimen. At times, the view through a good gastroscope would appear to be almost too revealing, when time, training, experience and study have not been blended in the examiner to make possible a mature evaluation. Under such circumstances, it is not too surprising that gross and histologic examination fail to confirm gastroscopic observation. Conversely, the lack of these same elements in the examiner may be the basis for failing to find and evaluate obvious pathology seen on x-ray examination. Too many failures with any procedure, in any locality, tend to discredit the procedure. It is unfortunate, but true, that there are areas where gastroscopy is looked upon as an inferior diagnostic method. Training and experience should do much to eliminate such incorrect estimates of an excellent diagnostic aid.

TRAINING

Training in any endoscopic method is difficult and hard to obtain. While short courses in orientation and theory are good and necessary, real training must consist of personal performance under the close supervision of an experienced endoscopist and teacher. Thus, training is difficult and time-consuming, for teacher as well as student. Although an undergraduate student or resident may, by chance, find the opportunity to perform gastroscopy during the course of his training, such occasions may be inadequately supervised or too few to be of real benefit. Frequently, it is not until after graduation that the doctor

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finds he has an interest in such work, a period when training entails a real sacrifice.

While there is, perhaps, no complete answer to this problem, we have attempted a partial solution by setting up weekly four-hour teaching sessions over a period of six months, limiting the class to one postgraduate student at a time, under direct supervision of a single instructor. Residents are trained in the same manner. Graduates of this system are not trained endoscopists, but have, so far, been in good position to add to their experience whenever possible, and, at the very least, have a better understanding of the method. More important, a few may, in time, be able to train others.

EQUIPMENT

The long flexible portion gastroscope with rubber tip is still standard, but modifications have added usefulness and helped to eliminate "blind spots". The controllable-tip instrument and Bernstein head² have allowed better visualization of the posterior wall and lesser curvature, although the distal antrum is still a problem. Poor visualization in this area may be eliminated in the future by use of the Fiberscope³, a mass of glass fibers which is completely flexible and transmits light to the eyepiece no matter how the instrument is bent. During the past five years, improvements on the Fiberscope have progressed to the point where it may be used routinely to view the stomach and duodenal bulb, as well as the small intestine through enterostomy openings. Time and experience will tell whether this instrument will supplant the gastroscope for routine examination, as claimed by some of its adherents, but its value and usefulness, especially in research, are obvious.

GASTROSCOPIC BIOPSY

While good gastric biopsies may be taken at random with a variety of instruments, such as the Woods, Shiner, and Rubin tubes, as well as the Crosby biopsy capsule, attempts to incorporate suction or forceps biopsy instruments into the flexible gastroscope have met with variable success. A truly directed biopsy is rare in our experience, although efforts are still continuing and success eventually should be achieved⁴. Directed biopsies are especially to be desired for complete correlation of gross gastroscopic and histological findings in specific areas of the stomach, as well as for correct diagnosis of particular lesions.

GASTROSCOPY AND ESOPHAGOSCOPY

Many gastroenterologists have, in recent years, become interested in the esophagus, and have applied endoscopy to this organ as well⁵. When performed together, the two endoscopic methods supplement each other in an excellent manner. If the results of x-ray examination are not available to the endoscopist, he may perform esophagoscopy and gastroscopy in that sequence. Since the

esophagus is traversed under direct vision, an extra safety factor is added to the subsequent gastroscopic examination. The performance of both methods is especially desirable if carcinoma of the stomach is suspected. A combined instrument is now available which makes it possible to do the gastroscopy with the esophagoscope in place, although some examiners, for technical reasons, prefer to do the two procedures separately.

GASTROSCOPIC PHOTOGRAPHY

While the demonstration of gastric pathology through the endoscope is a source of gratification to the gastroscopist, proof of what is seen has always been difficult to document. Color photography represents an ideal medium for this purpose. Excellent reproductions of visualized areas in the stomach may now be made with several types of apparatus. The two most commonly used employ increased light sources at the distal end of the instrument, one an electronic flash lamp, and the other a large tungsten bulb^{6,7}. The camera is attached at the eyepiece. Other types of equipment consisting of small cameras lowered into the stomach do not allow the operator to locate a field, and photographs must be taken blindly, a serious handicap⁸.

The gastroscopic features of various kinds of gastric pathology are now being routinely recorded⁹ for comparison with x-ray pictures, for teaching, and for proof of lesions not visualized by other means. Color photographs have proved especially valuable as teaching aids, and serve to impress particular features on students after live demonstrations and examination. They are indispensable as records in follow-up studies, and are entirely comparable, in their own way, to permanent x-ray films, having the advantage of being in color.

SPECIFIC USES

Gastroscopy is, in general, not employed enough. There is a persistent feeling that it should be used only to clarify a doubtful x-ray diagnosis, and the two methods do indeed complement each other in an ideal fashion. The routine use of gastroscopy to find lesions not seen by x-ray, where symptoms and signs indicate possible organic pathology, has been especially rewarding in our experience. Many lesions of all types have been found which were not located by other methods. If endoscopy is used often and expertly enough, the conclusion will be reached that, in most cases, evaluation of the stomach is incomplete without direct visualization of the mucosa. And if the examiner does not use the method often enough, he will not acquire or retain the requisite skill to gastroscop adequately. While accidents do occur, they are rare, and seldom attended with serious morbidity or mortality¹⁰.

Gastric ulcer:—The differentiation between benign and malignant ulcer can be made by evaluation of the gross gastroscopic and x-ray characteristics in the great majority of cases. In a recent survey¹¹, the two most frequent sources of

gastroscopic error were: 1. over-interpretation in the case of several large, benign lesions, and 2. failure to visualize a number of ulcerations on the lesser curvature of the antrum.

Eight of 100 ulcers in other parts of the stomach were found, however, only on gastroscopy. Direct inspection of the mucosa frequently revealed, in conjunction with ulcer, tumor which had not been identified by x-ray. This was true in several instances in which the ulcer itself could not be seen by endoscopy. In gastroscopic follow-up during a trial of healing, no carcinomatous ulcer has been seen to heal, although this has been reported on x-ray examination. Our present approach to the diagnosis of ulcer is routine gastroscopy, x-ray, and gastric Papanicolaou smears, which, we feel, will raise our accuracy to almost 100 per cent. With x-ray and endoscopy, it has been 96 per cent, and all carcinomas have had surgery.

Carcinoma:—The x-ray diagnosis of carcinoma of the stomach should be confirmed, whenever possible, by gastroscopy. If the suspected area is then well visualized and appears normal, another x-ray check should be carried out. A number of patients in our experience have been saved unnecessary surgery by this routine combination of procedures. Conversely, even when the x-ray examination is negative, gastroscopy should be performed if history or findings are suspicious of pathology. While carcinoma is seldom missed by the roentgenologist, cases will be found where the tumor is visible only on gastroscopy, especially when the mucosa is relatively intact. In training the endoscopist, opportunity should be given to view all possible carcinomas, since only in this way will the student become proficient in their detection.

Polyps and benign tumors:—The smaller polyps and benign tumors may frequently be missed by x-ray examination, and are often readily visible at gastroscopy¹². Adequate follow-up can be maintained by gastroscopy if immediate surgery is not desired, or is refused by the patient. Routine follow-up should eventually teach a great deal about the natural history of such lesions, and has been recommended in some cases for polyps¹³.

Gastritis:—While gastritis is a controversial subject at best, gastric atrophy, atrophic gastritis and hypertrophic or hyperplastic gastritis are best evaluated by gastroscopy. They are definite entities, even though their etiology and significance are, at present, obscure. The combination of gastric biopsy and endoscopy will in time clarify gastritis. Of practical significance is the giant hypertrophic or hyperplastic type, which may simulate tumor, but can, in most cases, be accurately differentiated by gastroscopy.

Foreign bodies:—Bezoars and other foreign bodies are most readily seen by endoscopy. While it is true that surgery is usually required for their removal, the patient may be reassured if there has been any question of the nature of the roentgenologically visualized tumor mass, and the surgeon is usually grateful to know exactly what he may expect to find.

Obstruction at the pylorus:—The cause of complete obstruction at the pylorus is often impossible to determine by x-ray. These patients should have thorough gastric lavage, following which gastroscopy will demonstrate, in a high proportion of cases, the presence or absence of tumor as a cause of obstruction. If tumor is present, surgery may be carried out as soon as the general condition of the patient permits, without any tedious trial waiting period. If no tumor is seen, conservative measures may be continued with a good chance of spontaneous relief of the obstruction.

Gastrointestinal hemorrhage:—The "vigorous diagnostic approach" has proven useful in many instances of upper gastrointestinal hemorrhage, especially in diffusely bleeding mucosal lesions. If esophagoscopy and gastroscopy fail to demonstrate a cause of hemorrhage, the source will usually be found below the pylorus, thus narrowing the range of diagnostic possibilities and allowing the surgeon to make an estimate of the procedure required.

SUMMARY

1. Since the development of the flexible gastroscope in 1932, gastroscopy has made rapid strides, and is now widely accepted as an excellent diagnostic aid. Better utilization of the method could be obtained if a larger number of trained endoscopists were available for diagnosis and teaching. A partial solution to this problem is suggested.

2. Improvement in instruments, and perfection of a new endoscope, the completely flexible Fiberscope, have eliminated most of the "blind spots" in the stomach. Gastrosopic color photography now allows complete documentation of findings, in a manner quite comparable to roentgenograms.

3. Gastroscopy is particularly useful in the evaluation of gastric ulcer, carcinoma, gastritis, gastrointestinal hemorrhage, and obstruction at the pylorus. Small benign and malignant tumors as well as foreign bodies, are more readily diagnosed by this method.

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HEMIGASTRECTOMY AND VAGOTOMY FOR THE TREATMENT OF DUODENAL ULCER*†

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In a search for the optimum surgical treatment for the complications of duodenal ulcer many technical procedures have been proposed. Most of these have a rational basis, but distal subtotal gastrectomy has remained the treatment of choice in most clinics. In recent years the reports of Edwards, et al¹, Smithwick, et al², and Palumbo, et al³ have suggested that the utilization of vagotomy in conjunction with a limited distal gastrectomy gives better protection from recurrent ulceration than other procedures used. Palumbo's report would also indicate that the incidence of postgastrectomy sequela was much less following vagotomy and antrectomy, though this has not been the experience of all investigators⁴. In our clinic subtotal gastrectomy has been a good, though not perfect, operation for duodenal ulcer and it was utilized almost exclusively until May of 1959. At that time it seemed that evaluation of hemigastrectomy and vagotomy was justified. The present report consists of a preliminary evaluation of the first 100 patients so treated between May of 1959 and November of 1960.

INDICATIONS

Hemigastrectomy and vagotomy has been used only for the treatment of duodenal ulcer, for gastric ulcer can be treated satisfactorily by limited gastrectomy. All of the 100 patients had long-standing chronic ulcer disease. In fact the average duration of symptoms at the time operation was performed was 11 years. Sixty per cent of these patients had bleeding as a major indication for operative intervention. Furthermore, 6 of these patients had required closure of a perforated ulcer previously. Thirty per cent had intractable pain as their primary symptom. Three (10 per cent) had previously required closure of an acute perforation. Obstruction was the indication in 9 per cent. Only 1 patient was treated for an acute perforation of a duodenal ulcer. Subtotal gastrectomy has remained the treatment of choice for this complication because of the fear of mediastinitis as a postoperative complication following vagotomy in the presence of peritonitis⁴.

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OPERATIVE PROCEDURE

Vagotomy was performed in the usual fashion, identifying the right and left vagus nerves and excising segments for histologic confirmation. The entire circumference of the esophagus was then stripped of all adventitia and smaller nerve filaments which might be present. A distal gastrectomy was performed, excising 50 per cent of the stomach. In some instances the amount of stomach excised was estimated by the surgeon, but in most, actual measurement of the specimen *in situ* with a sterile ruler was accomplished. The duodenal stump was closed in 99; a duodenostomy tube was placed in one instance. Gastrointestinal continuity was re-established by gastrojejunostomy; at times a Polya

TABLE I

A COMPARISON OF POSTOPERATIVE COMPLICATIONS FOLLOWING SUBTOTAL GASTRECTOMY WITH THOSE FOLLOWING HEMIGASTRECTOMY AND VAGOTOMY

Complication	Subtotal gastrectomy		Hemigastrectomy and vagotomy	
	No.	Per cent	No.	Per cent
Gastrointestinal bleeding	12	3.4	2	2.0
Leakage duodenal stump	10	3.4	4	4.0
Gastric retention	6	1.7	2	2.0
Subphrenic abscess	6	1.7	1	1.0
Intestinal obstruction	4	1.2	0	0.0
Splenic laceration	2	0.6	3	3.0
Esophageal laceration	0	0.0	1	1.0
Miscellaneous	14	4.3	0	0.0
Total	54	16.6	13	13.0

type was employed while in other instances the Hofmeister modification was used. In no instance was there an attempt to create an unusually small stoma.

MORTALITY

There were no deaths in this series.

POSTOPERATIVE COURSE

A factor of importance in the study concerned the resumption of bowel motility following vagotomy. To study this a comparison was made between the duration of nasogastric suction in a group of patients treated with subtotal

gastrectomy without vagotomy as compared to the length of time suction was required in these patients. The criterion for removal of the tube was the presence of bowel motility as demonstrated by auscultation of the abdomen and the passage of flatus per rectum. Suction was discontinued within 3 days in 90 per cent of the patients with subtotal gastrectomy, while in only 29 per cent of the patients in the hemigastrectomy and vagotomy group. The relatively longer period of nasogastric suction was the result of failure of motor activity of the entire bowel and was not related to stomal obstruction or specific absence of motility in the gastric remnant. The average time of nasogastric suction for patients in the subtotal gastrectomy group was 2.5 days as compared to 4.3 days in patients in the hemigastrectomy and vagotomy group. The slow resumption of normal bowel activity was also exemplified in the time required in the postoperative period before the patient was able to resume consumption of a soft diet. Most patients having simple gastrectomy were able to ingest a soft diet within one week postoperatively whereas more than 60 per cent of the patients with hemigastrectomy and vagotomy required 8 days or longer.

Despite the increased period of suction there was not a significant prolongation of total hospital stay in patients in the hemigastrectomy and vagotomy group as 45 per cent were discharged in less than 10 days and 75 per cent were discharged within 2 weeks.

INTRAABDOMINAL COMPLICATIONS

It was anticipated that the performance of a partial gastrectomy of limited extent would not significantly change the intraabdominal complications encountered as compared to those which occur following resection of 75 per cent of the stomach. Comparison with a group of patients having subtotal gastrectomy indicates that this was true. Of significance, however, was the fact that there was one esophageal laceration in the hemigastrectomy and vagotomy group, a technical complication not observed in patients with subtotal gastrectomy. This laceration was recognized at the time of operation. It was successfully repaired and did not contribute to the morbidity in the postoperative period.

Another technical complication observed more often in hemigastrectomy and vagotomy patients was splenic laceration. At times some mobilization of the spleen was necessary for adequate view of the esophageal hiatus, a maneuver unnecessary in subtotal gastrectomy. Resulting tears necessitated splenectomy.

There were only 2 patients in whom there appeared to be delayed emptying of the gastric remnant following resumption of small bowel motility, but the diagnosis is questionable in one of these for this patient was able to ingest a soft diet by the seventh postoperative day. In the second patient nasogastric suction was necessary for 16 days following which time the patient was able to take a liquid diet and rapidly progressed to normal food ingestion.

Other complications encountered were not significantly different from those seen following subtotal gastrectomy⁶ (Table I).

POSTGASTRECTOMY SEQUELA

Eighty-nine per cent of these patients have returned for follow-up visits at intervals ranging from 3 to 18 months postoperatively. This follow-up period is too short to allow definitive conclusions concerning the ultimate fate of these patients, particularly with regard to marginal ulceration, but the common post-gastrectomy symptoms usually appear within 3 months postoperatively and therefore observations of these symptoms are valid. In fact, one expects the highest incidence during this period for in some patients with postgastrectomy symptoms spontaneous remission occurs with the passage of time. The most common syndrome encountered in this group, as in patients with subtotal gastrectomy was the "dumping syndrome". This term refers only to that syn-

TABLE II

A COMPARISON OF INCIDENCE OF POSTGASTRECTOMY SYNDROMES FOLLOWING SUBTOTAL GASTRECTOMY AND FOLLOWING HEMIGASTRECTOMY AND VAGOTOMY

Syndrome	Subtotal gastrectomy		Hemigastrectomy and vagotomy	
	No.	Per cent	No.	Per cent
Small stomach	200	50	9	10
Dumping	144	36	24	27
Psychologic	4	1	1	1
Afferent loop obstruction	3	1	0	0
Hypoglycemic	2	1	1	1

drome occurring in the immediate postprandial period and associated with vasomotor as well as gastrointestinal symptoms. Twenty-four (27 per cent) of the 89 patients had symptoms which fell into this classification; however, they were mild in 14 and moderate in 10. There were no patients with severe symptoms (Tables II and III). Furthermore, 5 of the patients having moderate symptoms experienced this difficulty in the early postoperative period, but have had improvement even within the short period of follow-up noted here. This observation is favorable when compared to the incidence following subtotal gastrectomy for in that group the incidence has been 36 per cent or above and severe symptoms have occurred in approximately 2 per cent of patients³. In the hemigastrectomy and vagotomy group there was one patient having a psychosomatic syndrome requiring hospitalization and specific psychiatric care and one patient had the hypoglycemic syndrome. Thus far no patients have developed afferent or efferent loop obstruction. There has been one classical small bowel obstruction requiring operation.

An evaluation of weight change cannot be made accurately in these patients because loss of weight is common in the early postoperative period and many patients require at least a year to regain their preoperative weight. Thus an evaluation of the weight of these patients as compared to their preoperative status will indicate a higher incidence of weight loss than will be observed in the later postoperative course. Nevertheless, an evaluation of weight based upon normal weight-height charts indicates that only 10 per cent of patients lost as much as 5 pounds below their optimum weight, and in no patient was weight loss of sufficient magnitude to consider the result poor on the basis of this factor alone.

MARGINAL ULCERATION

No proven marginal ulcers have yet developed, but there are two patients in whom the clinical course has been strongly suggestive of the presence of

TABLE III
A COMPARISON OF THE SEVERITY OF THE "DUMPING SYNDROME" FOLLOWING
SUBTOTAL GASTRECTOMY AND HEMIGASTRECTOMY AND VAGOTOMY

Severity of symptoms	Subtotal gastrectomy		Hemigastrectomy and vagotomy	
	No.	Per cent	No.	Per cent
Mild	71	18	14	16
Moderate	64	16	10	11
Severe	9	2	0	0
Total	144	36	24	27

marginal ulceration. One of these patients has had gastrointestinal bleeding in the postoperative period. Thorough investigation including repeated upper gastrointestinal series, roentgenographic examination of the small bowel and colon, as well as gastroscopic examination has failed to demonstrate a marginal ulcer or other sites of bleeding. It is therefore possible that this patient has some other source of hemorrhage which is not yet demonstrated but until such is proven we consider him to have a suspected marginal ulcer. The second patient has experienced only pain suggestive of marginal ulceration. Again in this patient the diagnosis has not been confirmed objectively and it is made difficult by the fact that the patient has had intestinal obstruction, so that the diagnosis of partial obstruction without accumulation of gas in the small bowel has been considered as an explanation of his symptoms. It is of interest that both of these patients failed to demonstrate free gastric acid in the fasting state or after stimulation with histamine.

EVALUATION OF RESULTS

Because of the limited time for follow-up evaluation postoperative results cannot be considered final. At the present time 93 per cent of the patients have had good or excellent results. Two of the 6 patients classified as poor results are suspected of having marginal ulcer. Two patients with moderate postgastrectomy symptoms are classified as poor results. A fifth patient has a psychologic problem which requires therapy and one patient has no specific postgastrectomy symptoms but simply states that he is too weak to carry out his normal activities.

COMMENT

In this study gastrojejunostomy has been used exclusively for the reconstruction of gastrointestinal continuity for, a previous study in our clinic indicated that the Billroth I procedure was associated with a significantly higher incidence of marginal ulceration than the Billroth II. Utilizing hemigastrectomy and vagotomy Herrington did not find this difference between the two methods of reconstruction, but in view of the fact that the evidence to date suggests that the main advantage of hemigastrectomy and vagotomy is the decreased incidence of ulceration rather than a significant difference in postgastrectomy sequela this technic seems desirable².

We had anticipated that the addition of vagotomy to gastrectomy would result in the development of significant diarrhea in some patients; this complication, however, was not seen⁵.

In this study the incidence of postgastrectomy sequela is somewhat lower than we have encountered with subtotal gastrectomy, and it would indicate that the incidence may be significantly lower at the time of a 3- to 5-year follow-up. It was discouraging, however, to have 2 patients already suspected of marginal ulcer.

A further period of observation will be necessary to evaluate the procedure more adequately and to give a true comparison with the results obtained after other procedures. These short-term results, however, indicate that hemigastrectomy and vagotomy may be superior to subtotal gastrectomy.

SUMMARY

One hundred consecutive patients treated by hemigastrectomy and vagotomy for the complications of duodenal ulcer were studied. All patients survived the procedure. In the postoperative period nasogastric suction was required for longer periods than in patients with subtotal gastrectomy without vagotomy but the incidence of gastric retention as a specific problem was not increased. Eighty-nine patients have been followed for a period of from 3 to 18 months. In this limited follow-up 27 per cent had the dumping syndrome. Two patients are suspected of having marginal ulcer though the diagnosis has

not been proven. Ninety-three per cent of patients were classified as having good or excellent results.

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IN SITU pH OF GASTRIC CONTENTS IN PATIENTS WITH GASTRIC AND DUODENAL ULCERATION UNDER THERAPY*

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INTRODUCTION

In a previous communication Rossett¹ et al reported treatment schedules for gastric and duodenal ulceration designed to produce a pH of 3.0 or more during the treatment period day and night. Presumptive evidence was given that this was achieved. To confirm this more precisely we have, since January



Fig. 1—Intragastric electrode and tubing for KCl bridge.

1957, been recording around the clock the intragastric pH *in situ* of peptic ulcer patients undergoing treatment on these schedules.

METHOD

Patients in whom an active crater was demonstrated radiographically or by gastroscopy were selected at random from Medical Service and private patients

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of cooperating physicians at St. Joseph Hospital. The treatment schedules may be summarized as follows: Full breakfast, lunch, and supper from the usual convalescent ulcer diet are fed with the initiation of treatment. The antacid used was a suspension of 4 parts of aluminum hydroxide with 1 part of milk of magnesia in a minimum dose of 30 c.c. spaced at 2-hour intervals after meals and the preceding antacid dose through the entire day and night. An antisecretory agent was given 30 minutes before meals and at bedtime in a doubled dose. Antacids and secretion inhibitors were increased when necessary to produce a pH of 3 or greater as determined by intragastric pH recording or gastric aspiration 2 hours after feeding or medication.

We used the #78022V stomach glass electrode manufactured by Beckman and Company. It consists of a Ag-AgCl electrode immersed in N/10 HCl surrounded by a hydrogen ion permeable glass membrane approximately the

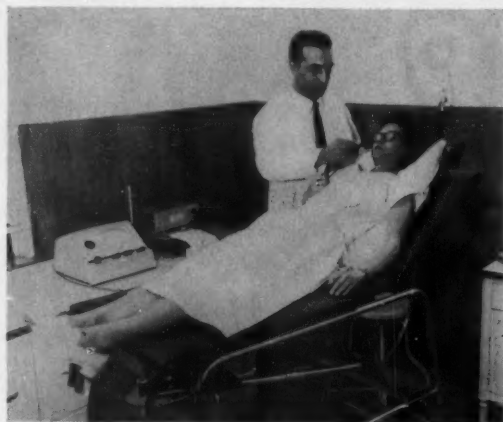


Fig. 2—Zeromatic pH meter and Varian recorder in operation.

size and shape of a match head. This is connected to a seven-foot length of flexible shielded cable which is 2 mm. in diameter. The assembly is easily passed through a patient's nostril into the stomach. When the electrode's correct position is confirmed fluoroscopically, a reference point is marked on the cable just outside the nostril in waterproof plastic tape, so that position can be maintained. The most consistent recordings were obtained when the bulb was placed in the most pendant portion of the stomach on the greater curvature with the torso at a 45 to 60° angle to the floor with the patient seated or in bed.

The Beckman #290 reference electrode was used. The cell itself consists of a Hg-Hg₂Cl₂ electrode surrounded by saturated KCl solution enclosed by a shell of high resistance glass. Contact is made through a small capillary tube plugged with asbestos fibers. We employed a 1 mm. polyethylene tube taped

to the cable of the glass electrode and passed into the stomach with it. This filled with saturated KCl served as a bridge to the indifferent electrode. Theoretically and empirically, this is the most accurate obviating varying potential differences between the forearm and the stomach mucosa. It was well tolerated by the patient. When recording, not infrequently, the regurgitation of small bubbles of gas into the tube would break contact in the system resulting in "hunt" in the recording equipment. The regurgitation could be prevented by continuous action on the part of a siphon assembly or by use of a hydrostatic column of saturated KCl 8 inches above the stomach level to permit continuous flow in the polyethylene tube which could be partially plugged to permit only a few c.c. per hour to pass. Another variation used the calomel cell connected by a special extension cord constructed of test lead cable plugged into the pH meter. The cell was then sandwiched between two 2 x 2 gauze sponges and the

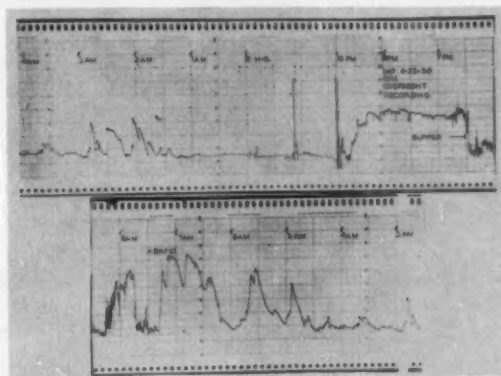


Fig. 3—Untreated active duodenal ulcer showing supper neutralization and acid secretion through the night.

sponges taped to the forearm. After moistening the sponges with saturated KCl, a 3 x 3 square of thin plastic sheeting was placed over the assembly and three sides sealed off with adhesive tape. The pads could then be checked and moistened occasionally with saturated KCl. The sheeting confined the KCl to a small area and evaporation was held to a minimum. We also used the reference cell connected to a bridge constructed of 4 mm. plastic tubing and a glass T-tube plugged at one end with cotton. The bridge was then filled with saturated KCl from a 20 c.c. hypodermic syringe and attached to the calomel cell with 4 mm. surgical tubing. Various parts of the body were used for attaching the bridge with a gauze sponge and adhesive tape. They were: 1. The forearm over the flexor muscles. 2. The deltoid region. 3. The buccal cavity. 4. The upper left quadrant of the abdomen. The forearm site was found to be the most comfortable for the patient, the most convenient for the operator and had no greater variation in pH from the gastric *in situ* KCl bridge than did the others. The

management of the bridge proved difficult because KCl solution seeped around the barrel of the syringe in spite of silicone "greasing" and KCl solution crystallized on the forearm producing some discomfort.

In 1954 we reported *in vitro* titration of antacids using commercial equipment then available². Less costly, equally efficient instruments are now marketed and for the experiments here reported we used a Beckman Zeromatic pH meter, Model 96 and a Varian Model G10 potentiometer recorder. The cost of our equipment was \$640.00. The newer instruments are lighter and smaller permitting easy transport for bedside recordings. Figure 1 shows the electrode and KCl bridge tubing to the indifferent electrode and Figure 2 the Beckman Zeromatic and the Varian Potentiometer recorder in operation.

Before each recording, calibration of the apparatus was checked with standard buffer solutions at a pH of 7 and 2.2. The response of the apparatus

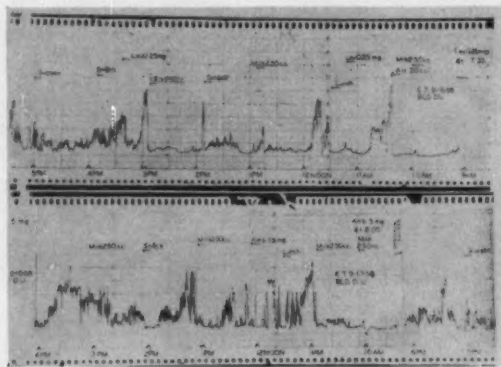


Fig. 4—Failure to effectively neutralize pH 3 or above with small feedings; Levsin® 0.25 mg. and Ambutonium® 5 mg.

was linear between a pH of 1 and 9. Sensitivity of the apparatus used was ± 0.01 pH. Medication used came from the Hospital Pharmacy as distributed on the wards.

RESULTS

We have successful recordings of more than 100 patients for over 2,000 hours. These will be reported in detail in another publication, while illustrative examples will be used here to show how a pH of 3 or greater can be achieved by varying antacid or anticholinergic agents according to the needs and response of the patient. Figure 3 illustrates the 6:30 P.M. neutralization of a full bland supper raising the pH to above 4 for about 2 hours. No medication was used. From 10:00 P.M. to 7:00 A.M. free HCl is present most of the time until 6:30 A.M. when a frequently observed phenomenon occurs of a decrease in

acidity until about 15 minutes before breakfast, which in contrast to supper, now neutralizes for only about 30 minutes. Figure 4 (upper graph) records the failure to neutralize free HCl, in a patient with a duodenal ulcer with hemorrhage who had ceased bleeding the day before recordings were started, using small feedings, an 8 ounce glass of milk a single dose of aluminum hydroxide

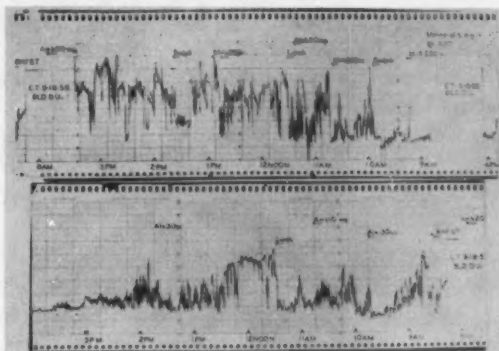


Fig. 5—pH 3 or better with 20 mg. Ambutonium®.

milk of magnesia*, l-hyoscyamine† in doses and at the times shown. There was improved neutralization on 9-17-58 (lower graph) by substituting 5 and 7.5 mg. of ambutonium bromide for l-hyoscyamine. Increasing ambutonium to 20 mg. in Figure 5 produces a decidedly improved response with the disappearance of free HCl. Reducing the ambutonium to 10 mg. results in failure to neutralize free HCl over an appreciable period. Figure 6 demonstrates neutralization with

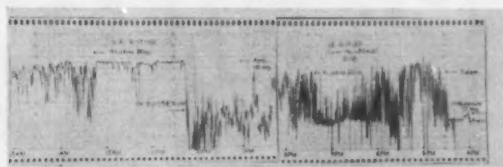


Fig. 6—pH above 3 in this patient with only 10 mg. Ambutonium®. Alakline pH when electrode slides into duodenum.

supper and 10 mg. of ambutonium and aluminum hydroxide-milk of magnesia suspension to a patient with an active ulcer. The suspension in a 30 c.c. dose continues the neutralization. Ambutonium 10 mg. alone fails to hold the pH above 3. When the duodenum is entered the pH rises above 7 and drops below only after additional antacid is given.

*Aludrox

†Levsin

COMMENT

A comparison of the first human intragastric *in situ* continuous pH recording^{3,4} with the present tracing reveals an absence of irregularities in the earlier tracing. Rovelstad⁵ was the first to record these rapid fluctuations in pH. The failure to show these rapid fluctuations previously rests on the electrical and mechanical inertia of the equipment available in 1940. The use of a saturated KCl bridge in a thin tube taped to the gastric electrode as used in the earliest recordings has proved to be entirely accurate whereas taking the indifferent electrode lead off the forearm is more convenient but introduces a small variable. How well and accurately equipment of this type can be used for the resolution of varying pharmacologic claims is illustrated by Robert Rubin et al⁶ and their work on acetylsalicylic acid and buffering's relative lack of effect on *in situ* gastric pH. It is the hope of the presentation that greater use will be made of the equipment and method.

Rovelstad used similar equipment to record also duodenal *in situ* pH. Our equipment works well in the duodenum. We hope to be able to report on simultaneous recordings of duodenal and gastric *in situ* pH. Rubin et al⁶ confirmed no interference in gastric recordings with a bare glass electrode in the stomach. In the duodenum the use of a cover guard to keep the electrode from contact with mucosa is necessary as Rovelstad⁵ has previously noted.

SUMMARY

1. Portable, relatively inexpensive available commercial equipment has been described for reliable, *in situ*, continuous, telemetering of intragastric and duodenal pH.

2. Previously described regimens for treating gastric and duodenal ulceration can achieve continuous 24-hour neutralization of the free HCl of gastric contents in patients with active ulceration.

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EXPERIENCES WITH DPA AND KIK IN THE GASTRIC JUICE OF PATIENTS WITH GASTRIC CANCER*

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Assuming that the constituents of gastric juice reflect gastric function, it would seem reasonable that some substance or substances in gastric juice might reflect gastric cancer either by specificity or by increased amounts of a normally occurring substance with the growth of tumor tissue. Also, it would appear that such material might be detected at an earlier stage than present methods for gastric cancer detection reveal.

Such changes have been sought for some time, and it has long been recognized that about three-fourths of cases of gastric carcinoma show either achlorhydria or a marked hypochlorhydria by ordinary fractional gastric analysis.

The development of new biochemical technics has resulted in a resurgent interest in gastric juice, particularly the mucus of gastric juice; yet, an obvious difficulty with the study of intestinal juices is that the material obtained by clinical methods represents a mixture of secretions of different glands; i.e., the gastric juice contains at least two different secretions, namely that of the surface epithelium and that of the chief neck cells⁶. This mixing tends to cloud the exact measurement of any single cell type function. Although, it is clear that the physiological function of the gastric juice is dependent on its characteristic physicochemical constituents and among these chemical properties is its mucus constituent. The investigation of the mucus secreted by the stomach mucosa has been mainly concerned with the isolation by chromatographic and electrophoretic methods of more or less well-defined mucoprotein fractions.

Glass and his associates^{7,11} have made significant contributions in this regard and have conclusively demonstrated that there are certain characteristic electrophoretic patterns associated with normal gastric function and gastric disease.

A normal pattern of gastric juice on paper electrophoresis demonstrates a leading anodic peak representing pepsin (P). The remaining anode components

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are made up of peaks numbered M1, M2, M3, etc., because they represent mucoproteins. On the cathode side, there is also a mucoprotein called M4 and a series of peaks labeled X, Y, Z, because their exact nature is poorly understood, although they are thought to represent some nondialyzable polypeptides which contain organic bases and may be degradation products of other high molecular components.

The two most anodic components of glandular origin, P and M1, are richest in protein and poor in carbohydrates; while the slow moving components, M2 and M4, and especially M3, all of surface epithelial origin, are richest in carbohydrates (hexoses, hexosamine, fucose). Component X contains hardly any carbohydrate, only a small amount of protein, and much nondialyzable material unidentified as yet. The most cathodic positively charged, Y and Z, do not contain proteins and carbohydrates at all¹¹.

Atrophy of the fundic glands had a characteristic compressed pattern with an absence of P and M1 and also of the Y and Z peaks. This is diagnostic for gastric atrophy if obtained after gastric stimulation, but does not differentiate pernicious anemia from atrophic gastritis^{7,9,10}.

In gastric cancer, a variety of patterns were noted depending upon the pathology of the coexisting adjacent gastric mucosa, although the atrophic pattern was most frequent. Another finding in an occasional case of gastric cancer was the passage of large amounts of serum albumin from the blood. This was also seen in some cases of atrophic gastritis and Menetrier's disease (giant hypertrophic gastritis). No pattern yet described is diagnostic of cancer^{9,10}.

Several studies on gastric juice and cancer have been reported from Japan^{13-16,19,21,22}.

For example, Sato¹⁹ noted that the mucin, especially mucoprotein, in the gastric juice of stomach cancer patients contained larger amounts of reducing substances than juice obtained from other kinds of gastric disease. He further reported that a "cancer toxin" which decreased liver catalase in mice was detectable in gastric cancer juice and that an agglutinin, which absorbed with kaolin, could be detected with antiserum in rabbits immunized with gastric cancer. Further, he states that amino nitrogens are present in higher concentrations. Unfortunately, there is a large overlap in the results between cancer and noncancer patients in his illustrations, but many of these observations would appear to warrant further investigation.

We have concentrated our attention on two other tests^{13-15,21,22} reported in the Japanese literature.

One of these¹³⁻¹⁵, called the KIK reaction, is named after three Japanese physicians who first described the test (Kozawa, Iwatarua and Kawagugi). These investigators observed that a subcutaneous injection into rabbits of gastric juice from stomach cancer patients resulted in a marked decrease in the

number of circulating rabbit's erythrocytes (20 per cent or greater) while gastric juice from healthy persons did not cause an erythropenia, but rather polycythemia. The material had been characterized as a mucopolysaccharide and mucoprotein. In the author's experience, this erythropenia was noted in 90 to 95 per cent of gastric cancer patients.

We repeated the test as described¹³⁻¹⁵ on 50 fasting specimens of gastric juice obtained from a variety of patients (Table I). A drop in red blood count was noted in all animals except six where a polycythemic reaction occurred. Five of the seven cancer patients gave a positive test as defined. Unfortunately, the controls and patients with benign disease, as well, had

TABLE I
KIK DETERMINATIONS OF GASTRIC JUICE
50 PATIENTS

% reduction of red blood cell count	7 Cases	27 Cases	11 Cases	5 Cases
80	O			
70				
60				
50				
40				
30		OO	OO	O
20	O OO	OO OOOOOO	OO O	O O
10	O O	OOOOOOO OOOOOOO	O OOO	O OO
0 or increase	O	OOO	OO	
	Gastric Ca	No Gastric Disease	Benign Peptic Ulcer	Miscellaneous

drops in blood count. From our experience, the test was not of differential value. The one case in which a marked drop in red cell count occurred is not explainable on the basis of any differences noted in the histology of the tumor or the patient.

We have sought for an explanation for the differences in our experience with the KIK test from the Japanese. One possibility might relate to different blood groups excreted in gastric juice in the Japanese gastric cancer patient that could cause destruction of rabbit's red cells. We have been unable to find reports regarding blood type in gastric cancer in Japan, but Tazaki²⁰ of the Japanese Cancer Institute reports that no hereditary influence has been recognized in gastric carcinoma.

A second possible explanation for the difference in reactions might relate to undefined difference in gastric cancer of Caucasians and Orientals. Also, a species difference in rabbits might be the critical factor.

A second test described by Wada, et al^{21,22} of Japan is the diphenylamine (DPA) reaction. This test was said to be 94 per cent accurate in gastric cancer with no false positive tests.

Diphenylamine is a colorless crystalline aniline compound which was noted by Dische^{4,5} to react with sugars that had been treated with concentrated mineral acids to form a purple color. Its use was first reported in this country by Niazi and State¹⁸ who noted that diphenylamine reagent (a mixture of glacial acetic acid, sulfuric acid and diphenylamine) when added to human serum produces a purple color. This color is measured with a spectrophotometer and is most intense in patients with malignancy, tuberculosis, cellulitis, rheumatic fever and subacute bacterial endocarditis.

The blood test has had its widest application in the evaluation of rheumatic fever where it was noted that the DPA serum index tended to parallel the clinical course of the disease in much the same manner as the sedimentation rate and the C reactive protein^{1-3,17}. There are reports to indicate that highest blood values are noted in patients with malignancy, particularly the lymphoproliferative disorders²³.

In the blood¹², the reaction has been associated with the serum protein containing carbohydrate moieties, particularly the glycoproteins of the alpha globulin fraction and is thought to be due to increased amounts of sialic acid.

Sialic acid is one of a group of naturally occurring carbohydrate acids which are ubiquitously distributed in tissues, having been identified as a constituent of lipids, of polysaccharides and mucoproteins. Normally, this acid occurs in high concentration in the blood while it is low in gastric juice^{6,11}.

In gastric juice²¹, the DPA chromogen was noted to be highest in the mucoprotein of M1 in acidic control and in M3 or M4 in the gastric carcinoma patient.

The DPA test²¹ consists of taking a filtered gastric juice specimen and boiling with trichloroacetic acid. The specimen is then filtered and the filtrate boiled with DPA reagent. A purple color is formed which is read in a spectrophotometer or a photometer with a filter of 530 mU. The blank used is the same gastric juice in which the DPA reagent has been withheld. The reaction is read in terms of optical density or Klett units.

We have performed this test on fasting gastric juice from 84 patients, 20 of which had gastric cancer. Those individuals without gastric disease fell below 300 Klett units O.D., but the overlap between benign and malignant disease was great and at least one and perhaps two false positive elevations were obtained (Table II). Five of the 20 carcinomas had low readings. A strongly positive reaction seemed quite indicative of carcinoma. In pernicious anemia

and achylia patients the values are not elevated, suggesting that the test is more than a reflection of atrophic gastritis.

Although not clear to us in the original report, a subsequent report²² suggested that a more distinctive dividing point between gastric cancer patients

TABLE II
DPA DETERMINATIONS OF FASTING GASTRIC JUICE
84 PATIENTS

Klett Units	20 Cases	17 Cases	13 Cases	5 Cases	6 Cases	15 Cases
1000	X XXX *					
900	X XXXXX					
800	X					
700	X					
600		X				
500	X					
400	X	X OOX	X O		X	
300	XX *	X XXOOOO	XX XXXXOO	XX	XX *	OOOOOO
200	X O	XXXX O	XX	XX X	OO X	OOOOOO O O
100						
0						
	Gastric Ca X—proven O—clinical course * polyps	Ulcer Benign Gastric Duodenal X—proven O—clinical course	Atrophic Mucosa X—pernicious anemia and achylia	Misc. X—Ca elsewhere O—Gastrointestinal bleeding, c.u. * pancreatitis	No gastric disease	

and other groups could be noted when the specimen of gastric juice tested was obtained 40 minutes after an intravenous injection of 15 units of regular insulin. From Wada's²³ graphs it would appear that this chromogen increases in amounts following insulin stimulation in cancer, but decreases in normals and persons with other gastric diseases. The latter situation may represent a dilution factor from gastric secretion following insulin stimulation.

It would appear that cancer produces an increased amount of the DPA chromogen. Such increases in the blood are obviously not specific for cancer,

but in gastric juice which is more reflective of gastric function, the test would appear to have more specificity. At any rate, a marked rise in gastric juice values would appear diagnostic of gastric cancer, although the presence of normal values in fasting specimens does not exclude a malignancy.

We are continuing this work with serial specimens following insulin stimulation, but our studies are too few at this time for an opinion.

There are numerous fractions that make up the mixture of glycoproteins demonstrable in the polysaccharide protein complex of gastric mucin. It would appear that a systematic study of these substances might reveal distinctive patterns associated with different types of gastric disease. Among such patterns might lie a simple and early diagnostic test for gastric cancer.

SUMMARY

The fasting gastric juice of patients with a variety of conditions was analyzed with two tests reported in the Japanese literature to have a high degree of specificity for gastric cancer. These tests are the KIK reaction and the DPA reaction.

The KIK reaction is a biological test in which gastric juice from gastric cancer patients had been reported to produce a drop in circulating rabbit erythrocytes of 20 per cent or greater when injected subcutaneously, while in normals a polycythemia was said to occur. This test was performed on 50 specimens of gastric juice. Five of seven gastric cancer patients gave a positive test as defined, but a similar drop was noted in 17 of 27 patients without gastric disease, 6 of 11 cases with benign ulcer and 2 of 5 patients with miscellaneous conditions.

The DPA reaction is based on the principle that diphenylamine reacts with sugars that have been treated with a concentrated mineral acid to form a purple color. The color produced can be read with a photometer with a filter of 530 mU. Using gastric juice, elevated values had been noted in 94 per cent of gastric cancer patients in Japan. This test was performed on fasting gastric juice in 84 patients. Thirteen of 20 gastric cancer patients had values greater than 400 Klett units, the remaining 64 patients with a variety of gastric disorders all had values below 400 units except one case of proven benign gastric ulcer. While in our experience, the test was only 65 per cent positive (values > 400 Klett units), elevated values appeared to be strong evidence for gastric cancer.

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LABORATORY AIDS IN GASTRIC DISEASE*

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The stomach is an organ which most of us use at least several times daily, as it is useful for the purpose intended. It is an organ which serves us throughout life and it is rare indeed to find a person who has not at one time or another complained of stress originating here.

The stomach, of course, is under involuntary control and no society escapes a great incidence of functional disease from this organ. It is also the seat of one of the more common cancers of mankind. The stomach is subject to influences from many of the generalized diseases, including such diseases as tuberculosis, syphilis, and a wide variety of acute inflammations. Indeed, the gastritides have plagued the radiologist, gastroenterologist and pathologist, who can't agree as to the true nature and symptomatology of gastritis. Among its many diseases, one must mention that gastric ulcer is quite common. The recent finding of such a lesion demands that a differentiation be made between benign and malignant disease. To help solve the many problems in diagnosis of both functional and organic disease of the stomach, the clinician has at his disposal several laboratory aids. It is the purpose of this paper to comment upon the reliability and accuracy of these procedures.

A well-taken history and physical examination often will suggest the presence of possible disease of the stomach and will usually indicate which procedures are most appropriate to solve the particular problem presented. Two procedures, however, are of value in screening for disease of this organ, even when no disease is suspected. The first of these is the examination of the stools for occult blood. This is emphasized at this point only because it is frequently overlooked. It is an excellent screening test for organic disease of the stomach, although not specific. Examination of the stomach by x-ray is also an excellent method, and in fact one of our best procedures for both screening purposes and for defining more exactly the nature of disease of this organ. It should be emphasized, however, that a gastrointestinal series is only as adequate as either of the two participants allow it to be. First of all, the training, care, time and interest of the radiologist are of utmost importance. Secondly, the cooperation of the patient is required and is equally as important in the final determination of many of the lesions of this organ. Even though the x-ray examination of the

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stomach is one of our most accurate, the most competent radiologist will miss some organic pathology. It should be realized that in incompetent hands an upper gastrointestinal examination serves only to irradiate the patient and to give a false sense of security to the clinician. Few examinations are more challenging than this and it should be emphasized that a single examination may only serve to alert attention to a certain area of the stomach. When this is the case, or even following a negative gastrointestinal series, if the clinical findings still suggest disease in this area, a repeat examination should be done. Not getting the second and third examination when indicated is probably the greatest failing in diagnosis of gastric disease, the point being that seldom can one examination be adequate to thoroughly investigate all aspects of this rather sizable organ.

Of recent help, not yet used much at clinical levels, has been the development of cinefluorography. With the development of greatly improved fluoroscopy intensification and transmission by television, cinefluorography is being used with benefit for: 1. training the radiologist, 2. educating the physician, and 3. opening new vistas for clinical research.

Gastroscoy is useful in the study of gastric disease, especially when disease is suspected on the x-ray examination. Several points are worth mentioning as regards gastroscoy. First of all, again a competent endoscopist is as important as a competent radiologist for the x-ray examination. Also, present day gastroscoy is done through a closed tube, which unlike the esophagoscope (which is open) does not allow for instrumentation. The gastroscope is a rather delicate and intricate optical instrument. There are several instruments marketed which vary in their advantages, each different instrument having a special feature such as one is accustomed to finding when shopping for a new washing machine. Thus, the Cameron gastroscope has omniangle attachment, which allows one to expand the field of vision. The Schindler gastroscope is quite flexible and is able to be passed at times when other gastroscopes fail. The Eder gastroscope has a changeable focal distance so that one can observe lesions which are sitting just in front of the lens, not possible on most other scopes, and the Benedict gastroscope allows one to take biopsy tissue under observation. Notwithstanding these features, it should be mentioned that about one-fifth to one-quarter of the stomach is "blind" to gastroscopic examination, and this includes primarily: 1. the posterior wall, 2. parts of the cardia, 3. parts of the antrum and pylorus, and areas of the lower pole of the stomach. At present, work is being done to develop a gastroscope made of fiberglass or other materials which will increase the flexibility and thus allow better vision of these blind areas.

One of the most promising present movements in this field has been the development of reliable gastric cytology. In this case, exacting technic is imperative and the reading of slides for malignant cells is laborious and time-consuming. When available, however, and adequately performed, gastric cytol-

ogy is of tremendous help in reassuring both the patient and the physician that malignant disease is not present. Of course, a few other organic diseases—such as pernicious anemia—can be diagnosed by this means, but its main advantage is screening for malignant disease.

Gastric acidity as an examination has had many ups and downs in recent decades. There is a great variation of opinion among physicians concerning the value of a gastric analysis. Some competent gastroenterologists publicly state that they have never derived any advantage from a gastric analysis other than for the diagnosis of pernicious anemia. Some believe that gastric analysis should be a routine part of the complete physical examination. Probably a great deal of the misunderstanding has developed in this field because the examination was inadequately understood or performed, or the physician did not have an adequate conception of what he desired to find out from the examination. Thus, the following questions can usually be answered by adequate gastric analysis—to wit: Does the patient have achlorhydria? Does the patient have a duodenal ulcer? Is a vagotomy complete? Is the stomach emptying? Is there hypo- or hypersecretion? It is, however, only of help in conjunction with other tests of gastric function. In this regard, it should be mentioned, however, that when one desires to know whether or not any acidity is present, it is necessary to maximally stimulate the gastric acidity, which is generally done by the injection of histalog, maximal stimulation occurring about three to four hours following injection. A procedure which does not allow this length of time and does not get multiple samples, will not necessarily answer the question as to whether or not acidity is present. On the other hand, some test of gastric acidity, such as the Ewald meal, is helpful because of other reasons, it giving an idea both of gastric acidity (though not a most accurate test in this regard), but also giving an idea of whether or not the stomach empties properly. On the other hand, the insulin stimulating gastric analysis, although difficult to perform, is the one gastric analysis best suited to indicate the adequacy of a vagotomy.

Along these same lines, blood and urine pepsinogen levels have been championed as one method to investigate function of the stomach without having the patient suffer from swallowing a tube. In general, it is the authors' impression that although this is of mild usefulness in some patients—that is, when the blood pepsinogen level is high and there is gastric function present—the negative test is of no value and is frequent enough to greatly diminish the usefulness of this tool as an aid in gastric diagnosis. On the other hand, the so-called tubeless gastric analysis was also developed several years ago in an effort to avoid the tube but determine the presence or absence of acid. Again the correlation is poor and the authors have abandoned using this test, except on the rare occasions when the patient adamantly refuses to swallow a tube and it is quite important to establish the possible presence of acidity in order to help rule out a diagnosis of pernicious anemia. A negative test, however, is valueless.

Another method for exact diagnosis is by blind biopsy tubes. Dr. Woods introduced the so-called "Woods tube" which allows one to take a blind specimen from the esophagus, stomach, or even early duodenum. Dr. Shiner, also of the British Empire, developed a tube which passed "blindly" and through which multiple biopsies can be taken. This has been manufactured in Seattle, Wash., where it is being championed by Dr. Cyrus Rubin (hence the name "Rubin tube") which has the advantage of having a small bore, of being more flexible, of entering the small bowel easier, plus being usable on the stomach or esophagus.

Some of the greatest help in recent years has been derived from the so-called Schilling test, designed to test Vitamin B₁₂ absorption and used primarily in the diagnosis of pernicious anemia, but also a useful method of diagnosing gastric atrophy (which inevitably is present with pernicious anemia) and malabsorption syndrome. As a gastric test, it is helpful when positive in alerting the physician to the presence of gastric atrophy, and alerting him further to the increased incidence of carcinoma found in this disease.

Another test, seldom performed but of some benefit in the occasional patient, is the so-called "acid test", in which a small bore tube is placed in the desired position (esophagus, stomach, or duodenum) and the area is washed with a benign solution such as saline, or even bicarbonate. Next, a very dilute solution of acid is injected into the evacuated area, and should typical pain occur or recur during this procedure the presence of ulceration in the area is strongly substantiated. Also of some occasional benefit in the presence of bleeding from an unknown site in the gastrointestinal tract, is the so-called "string test" in which a string is swallowed a measured distance and upon withdrawal the string is tested with benzidine (for blood) and the highest level obtained positive for blood indicates the probable site of gastrointestinal bleeding. A small bore polyethylene tube is also helpful in this regard.

In conclusion, it can be said that in no area of investigation is the good understanding and exacting and adequate examination as important as in the study of gastric disease. Any of these tests, done inaccurately, are worthless, but when all of these tests are used and accurately performed, two conclusions are justified: 1. the patient will be broke, and 2. the physician will be completely bewildered by the results.

TRIALS AND TRIBULATIONS IN THE TREATMENT OF INTESTINAL PARASITIC DISEASE*

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All too frequently the physician is confronted with a case of parasitic infection, and he is at a loss for a proper therapy.

The problem has become increasingly important in the United States¹ since the second World War², after our troops had served in far flung areas of the world³, where parasitic diseases were endemic⁴ and wide spread. The vast increase in interregional travel and the immigration to our shores of people from tropical lands⁵, has likewise added to the incidence in our midst⁶.

The number and variety of cases encountered is on the increase and bids fair to become a great communal public health⁶¹ as well as personal health situation. How then, to handle parasitic infestation individually and collectively is the question for discussion^{7,8}?

Although parasitic disease has plagued mankind since primitive times, no concrete or comprehensive plan has yet been devised to treat, let alone prevent, its occurrence and spread. Until recently, there were only a few satisfactory drugs available. In the past several years, however, great advances have been made in chemotherapy⁹⁻¹³.

Some drugs of proved value have been discontinued, since in full therapeutic doses they had too narrow a margin of safety. This is especially true in the malnourished, very young and very old, who seem to be the majority of those afflicted with parasitic disease. Thus, drugs such as thymol, santonin, carbon tetrachloride, chenopodium and others have already been discarded by most parasitologists. Some drugs such as emetine, although still widely used and praised by many¹⁴⁻¹⁶, as the most valuable single drug in amebiasis, should also be discontinued, according to some workers in the field^{17,18}, because of its many toxic effects.

In the treatment of helminthic disease, we have a drug of choice for each parasite. In the treatment of amebiasis, however, there are at least a dozen drugs of relative efficacy^{19,20}. The location, and degree of the infection or infestation, and the general condition of the patient will determine to a great extent, the drug or drugs of choice to be used as well as the mode of administration²¹. Even at the present time, it is not feasible to outline a routine treatment and

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management for all patients. Before treatment is started each patient must be carefully evaluated as to the infecting parasite, grade and location of infestation, as well as his possible systemic toxic reactions. Many patients may have so mild a disease, as in some cases of giardiasis and trichiuriasis, that no treatment other than good hygiene is necessary²¹. Others, more seriously afflicted may require a great deal of supportive therapy such as parenteral fluids (in severe diarrhea), blood transfusions and iron therapy (in hookworm disease), Vitamin B₁₂ and B-complex in *dibothriocephalus latus*²². In acute fulminating amebic dysentery, where dehydration, diarrhea and cramps are generally present, antidiarrheal drugs for symptomatic relief and replacement of fluid balance may be most urgent, before specific antiamebic therapy is initiated. Antibiotics would definitely be contraindicated as a specific drug here, since "the cure may be worse than the disease". It is well known that terramycin, achromycin and aureomycin may cause abdominal cramps, severe diarrhea, pruritus, and the dreaded pseudomembranous enterocolitis with occasional death. In severe hookworm disease and in marked infestation with other helminths, where severe anemia, malnutrition and avitaminosis are pronounced, grave consequences may result if specific therapy is instituted before blood and vitamin replacement has taken place. Diet, vitamins, as well as symptomatic treatment must be part of any therapeutic regimen.

In cases of multiple infestation it is important to determine which parasite is most disturbing to the patient and then attack it first.

In the multiple infection with both ascaris and hookworm, however, it is necessary to eradicate the ascaris first before treatment for hookworm with tetrachlorethylene is commenced. It has been claimed for some time²³ although denied lately²³ that tetrachlorethylene stimulates the growth of ascaris to such proportions that large boli of these worms, with their irritating effect on the bowel mucosa, may cause intestinal obstruction and even perforation²⁴.

Keeping these deterrents to routine treatment of intestinal parasitosis in mind, we present a brief outline of drugs presently employed in treatment, with suggested dosage and method of use. If a full course of therapy fails to produce results, a second course of the same or another drug or a combination of drugs may have to be used^{9,25}.

AMEBIASIS

Amebiasis is still the most prevalent parasite encountered here²⁶ and in other countries²⁷. In representative surveys in the United States, a conservative estimate shows that at least 10 per cent of the population is infected with *Endameba histolytica*. Amebiasis is a generalized disease and its manifestations are protean^{27,31}, depending upon which tissue of the body is involved and to what extent. For the purpose of treatment, amebiasis may be separated into intestinal and extraintestinal infection. In some cases the ameba attacks the bowel only

(intestinal). Some of these cases may develop amebic hepatitis and liver abscess. Extension of the latter through the diaphragm may lead to pleuropulmonary infection. Even brain abscess with the ameba as the infecting organism has been reported. Although surgical intervention in some cases of liver or pleuropulmonary abscess and ameboma is at times indicated^{25,31,32}, open surgery is rarely resorted to now³³⁻³⁵ because of the high mortality rate. Treatment of amebic liver abscess at present consists of a full course of either emetine HCl or chloroquin³⁶. If no improvement is seen, the abscess is drained by aspiration, and chloroquin or an antibiotic is instilled into the cavity. An intestinal amebicide should be used at the same time in an attack on the ameba in the intestines. Radke³⁴ has successfully treated 15 cases of liver abscess with atabrine and carbarsone. His treatment consisted of atabrine, 0.1 gm. four times daily for 30 days and carbarsone .25 gm. tablets, two times daily for 10 days. In pleuropulmonary amebiasis conservative therapy with antiamebic drugs will, in many cases, bring dramatic improvement. Thoracotomy should only be used as the last resort^{35,31}.

It has been pointed out that the ameba (*in vitro*) grows only in the presence of bacteria³⁷. It is, therefore, no accident that antibiotics and sulfonamides are found useful either as adjuncts to, or as the specific drug in the treatment of amebiasis. It must be kept in mind, however, that drugs such as aureomycin, terramycin^{30,38} and achromycin, while beneficial in the treatment of amebiasis, may cause abdominal pain, nausea, vomiting, diarrhea and severe pruritus. These side-effects, obviously may be more troublesome to the patient than the ameba itself. One must also keep in mind the ever-threatening appearance of pseudomembranous enterocolitis, where full doses of antibiotics are employed. Penicillin and streptomycin, too, have their usefulness as adjuncts to specific therapy in amebiasis. Finally, bacitracin²⁰ has to be mentioned but is not recommended. Although it has been a good drug in some cases where other drugs have failed, its toxic effects on the kidney preclude its general use.

EMETINE HYDROCHLORIDE

As mentioned before, emetine is a powerful agent. It has a low rate of absolute cure (30 per cent) and is extremely toxic, affecting the cardiovascular, nervous and gastrointestinal systems. It should, therefore, be used with caution and not on an ambulatory basis. A daily ECG is essential. It should never be given in the very young, or in patients with cardiac or renal disease, or during pregnancy. Emetine is especially useful in acute dysentery and in hepatic amebiasis. The generally accepted dose is grain 1 daily intramuscularly, (never intravenously or subcutaneously) for 10 to 12 doses. Because of its toxic and possible cumulative effects, a period of one month should elapse before the dose is repeated. Emetine bismuth iodine (29 per cent emetine, 12 per cent bismuth, 58 per cent iodine) is used extensively in many areas of the world. It has the same drawbacks in its use as emetine.

FUMAGILLIN

Fumagillin (derived from a culture of *aspergillus fumigatus*) is an active amebicide in high dilution, *in vitro*^{10,11}, and has been found especially effective in nondysenteric amebiasis³⁹. It comes in 10 mg. capsules and is given 60 mg. daily in divided doses for 10 days. It may be repeated if the first course is in-

TABLE I
OUTLINE OF DRUGS USED IN TREATMENT OF AMEBIASIS

Drug	Tissue involvement	Dosage	Duration
Carbarsone	Intestinal amebiasis	One 0.25 gm. tab. b.i.d.	10 days
Milibis	Intestinal amebiasis	0.5 gm. tab. t.i.d.	7 days
Diodoquin	Intestinal amebiasis	Adult 0.65 mg. t.i.d. Children 0.21 mg. tab. t.i.d.	20 days 10-20 days
Vioform	Intestinal amebiasis	0.25 gm. tab. q.i.d.	10 days
Chinofon	Intestinal amebiasis	1 gm. t.i.d.	10 days
Chloroquin	Extraintestinal amebiasis (Liver abscess, etc.)	0.3 gm. b.i.d. 0.3 gm. daily	2 days for additional 12-19 days
Camoquin	Extraintestinal amebiasis	0.6 gm. tab. t.i.d.	10 days
Camoform	Carrier and acute dysentery	0.5 gm. tab. t.i.d.	5-7 days
Fumagillin	Intestinal amebiasis	20 mg. t.i.d.	10 days
Atabrine	1. Intestinal amebiasis 2. Extraintestinal amebiasis (liver abscess)	0.2 gm. q.d. 0.1 gm. t.i.d. in combination with 0.25 gm. b.i.d.	10 days 30 days for the first 10 days
Emetine HCl	In acute fulminating intestinal amebiasis and in amebic hepatitis and/or abscess	1 gr. i.m.	10-12 days

effective as it is comparatively nontoxic. It has occasional side-effects such as mild nausea, vomiting and diarrhea. Cases of leukopenia and bone marrow depression have been reported in its use^{40,41}. Although useful by itself or in combination with other drugs, fumagillin is difficult to obtain in the United States.

DIDOQUIN

If there were one drug of choice in the treatment of amebiasis, it would be Didoquin. (Supplied in .21 grain tablets.) It has no known toxicity or any systemic side-effects except for an occasional mild headache. It is extremely effective in acute intestinal cases. It is given in 2 or 3 tablet doses three times daily for 10-20 days. In children the dose is one tablet daily for every 15 lbs. in weight for 10-20 days.

CHINOFON AND VIOFORM

These are useful amebicides but are intestinal irritants and contraindicated in iodine-sensitive individuals.

CHLOROQUIN

This [(aralen) comes in .25 gm. tablets] is an aminoquinilone which concentrates in the liver and is thus very effective in amebic hepatitis³⁶ and liver abscess. It is less effective in intestinal cases. It is given one tablet (.25 gm.) b.i.d. for 2 weeks. It may cause some mild side-effects such as headache, pruritus, and visual disturbances, which should not cause discontinuance of the drug.

CAMOQUIN

Camoquin (amodiaquin) is also most useful in extraintestinal amebiasis, but has no advantage over chloroquin.

CAMOFORM

Camoform (bisphenol) is an active agent against all forms of amebiasis, but has many side-effects and is not extensively used.

CARBARSONE

Carbarsone (a pentavalent arsenical) is a very effective amebicide and generally causes no ill effects in therapeutic doses (.25 gm. tablets 4 times daily for 10 days.) It is especially useful in treatment of intestinal amebiasis and carriers. Although a very valuable drug, it is an arsenical, and it should not be used in presence of liver and kidney disease.

MILIBIS

Milibis (bismuth glycolylarsenilate), like Carbarsone is an effective intestinal amebicide. It comes in .5 gm. tablets. Dose is 1 tablet 3 times daily for 14 days.

ATABRINE

Atabrine (quinacrine HCl) is especially useful in amebic liver abscess³³. Dose in liver abscess, .1 gm. q.i.d. for 30 days. Combine with Carbarsone .25 gm. tablet for 10 days.

GLAUCARUBIN

Glaucarubin (extract from the *simaruba amore* plant) is a glycoside active in both intestinal and extraintestinal infections¹⁵. It is nontoxic. Daily doses may vary from 10 to 280 mg., given from 5 to 32 days. It is being used extensively in Mexico, but as yet has not been used in the United States. Generally speaking, Diodoquin in combination with Carbarsone will cure the great majority of cases of amebic diseases (Table I).

HELMINTHS

In the treatment of parasitic helminths in man, no universal anthelmintic has yet been discovered. Indeed, as mentioned before, whereas tetrachloroethylene is extremely effective in hookworm, it stimulates the growth of ascaris²². One or more of a number of drugs may be used to obtain similar end results. It is worth repeating here that, according to most parasitologists, not in every patient in whom the presence of intestinal parasitosis is discovered, is treatment indicated.

Giardia lamblia, although a flagellate, is grouped under helminthic disease because it is generally found coexistent with the helminths. In itself it is not a tissue invader and rarely causes symptoms. When present in large numbers in the region of the duodenum it may cause symptoms of biliary disease with epigastric distress, nausea, belching and sometimes diarrhea. Treatment consists of atabrine 1 tablet, 3 times daily for 1 day and one b.i.d. for 7 days¹⁶. The dose may be repeated after a few days. Mild infection with *Trichuris* and even with *Strongyloides* and hookworm may go untreated if proper sanitary precautions are taken. The schistosome, however, presents a special problem. Here, as soon as the diagnosis is made, or even only strongly suggested, treatment must be started immediately. The schistosome, although considered an intestinal parasite, does most of the damage as a blood parasite. The larvae after penetrating the skin, find their way into the circulation and reach the portal veins. There they mature and migrate against the flow in the hemorrhoidal vessels and penetrate the wall of the colon and rectum. Some get caught in the wall of the bowel (helping in diagnosis when ova and parasites are absent in the stool)¹⁶, while others get swept back into the portal venules and form pseudotubercles in the liver, which in time lead to liver fibrosis. Portal obstruction with hepatosplenomegaly and cirrhosis of the liver may be the end result. Thus the first complaint in schistosome infection may be sudden and severe gastrointestinal bleeding from esophageal varices. It is evident that once portal cirrhosis is established in advanced schistosomiasis, treatment will have to be directed to relieve ascites by periodic paracentesis or portacaval shunt. Supportive therapy and treatment for hepatic failure may have to be instituted instead of, or in addition to specific therapy, which many of these patients stand poorly.

Incomplete treatment in parasitic infection, may merely inhibit ova production and result in the patients becoming carriers and often lead to reinfection.

Since all the tapeworms possess a mechanism by which they securely attach themselves to the intestinal wall of the host, it is important in the treatment of cestodes to search for the scolex or head of the worm, when extruded in order to be certain of cure. Large worms such as ascaris and tapeworm may produce partial or acute intestinal obstruction and in ascaris, even, perforation of the bowel²⁴. Here, it is obvious that treatment of intestinal obstruction or definitive surgery will have to be resorted to, before specific therapy would be undertaken. If partial obstruction is overcome by means of Wangensteen suction and fluid replacement, specific therapy may be introduced through the Levin tube which is already in place.

In *Strongyloides*, systemic toxemia is indicated by giant urticaria and a high eosinophil count and occasional Loeffler's pneumonitis, may have to receive primary attention before or during specific anthelmintic therapy.

In pinworm disease, a separate problem arises in treatment, because of the very annoying symptoms resulting from migrating females at the anal canal. Scratching caused by the pruritus will cause local irritation with eczema and secondary pyogenic infection of the region, as well as tenesmus and rectal colic. Poor appetite, loss of weight, anemia and emotional irritability are other aspects of the infection that may require the attention of the attending physician. Jenkins⁴² successfully treated 20 out of 25 cases of pinworm disease with zinc oxide ointment. He applied the ointment, 1/4 inch thick, about the anus and perianal folds three times daily and at bed time for 21 days. This, however, is not generally accepted as complete treatment for pinworm disease but may be used together with more specific helminthics.

Trichinella spiralis:—A search for a good anthelmintic to kill the larvae in the muscle has not yet been found. Nor has any success been had with expelling the adult worm from the intestines²¹. Hetrazan and Piperazine have shown some promise in experimental animals. The treatment at present is symptomatic with ACTH to help in the allergic manifestations.

SPECIFIC DRUGS AND MODE OF USE IN TREATMENT OF HELMINTHS

1. *Dithiazanine*^{7,44}:—(Delvex, Telmid)—100 mg. tablets, 100 to 200 mg. t.i.d. for 5 to 10 days. It is nontoxic and can be repeated after a few days.

2. *Quinacrine HCl*^{7,15,18}:—(Atabrine) .1 gm. tablets. In Giardiasis one tablet 5 times daily for 1st day. Followed by 1 tablet t.i.d. for 7 days⁶. In tape worm disease^{7,16,43} it may be given either orally or by duodenal intubation.

a. *Oral medication* is given in the morning on an empty stomach. Oral—1 tab. (.1 gm.) every 2 minutes until 10 tablets are taken. (Compazine or sodium bicarbonate may have to be given to lessen nausea or vomiting). Two hours later a saline purge is given. This treatment may be repeated a week later.

b. By intubation:—One gm. of the medication is prepared by soaking 10 (.1 gm.) tablets in water overnight. A Levin tube is passed into the duodenum in the morning before breakfast, the medication (1 gm.) is instilled and the tube withdrawn. This is followed by a saline purge 2 hours later. Food should be withheld until after a bowel movement. Yellow discoloration of the skin may be expected to follow treatment.

TABLE II
PARASITE AND DRUG OF CHOICE

Parasite	Drug of choice	Second choice	Other effective drugs or methods
Tenia Saginata	Quinacrine	Oleoresin of aspidium	Hexylresorcinol
Solium	Quinacrine	Hexylresorcinol	
Dibothriocephalus	Quinacrine	Hexylresorcinol	
Trichiuris Whip	Dithiazanine	Dilombrin	Hexylresorcinol enemata
Trichinella	Piperazine (may be tried)	Hetrazan (may be tried)	ACTH (symptomatic)
Enterobius Oxyuris vermicularis (pin worm)	Piperazine citrate hydrate Pomade	Dithiazanine	Gentian violet
Ascaris	Piperazine	Hexylresorcinol	Lêche de Higuéron
Hookworm	Tetrachlorethylene	Bephinium (Alcapar)	Hetrazan
Strongyloides	Dithiazanine	Gentian violet	Hexylresorcinol and Hetrazan
Schistosoma Mansoni	Fuadin	Tartar emetic	(Miracil) Thioxanthrone
Schistosoma Hematobium	Fuadin	Tartar emetic	
Schistosoma Japonicum	Tartar emetic	Fuadin	

3. *Tetrachlorethylene*^{7,15,21}:—(1 c.c. capsules)—Give a purgative the night before. Adult dose—3 capsules on an empty stomach—2 hours later give saline purge. Withhold food until bowels have moved. This treatment should be given with patient lying in bed or sitting for at least 2 hours after medication has been taken. Treatment may be repeated at 4-day intervals.

4. *Oleoresin of aspidium*^{7,18,21}:—(Felix Mass)—0.6 c.c. capsules. Purgative the night before.

a. Orally:—Two capsules every half hour for 3 doses, on an empty stomach. Purgative 2 hours after medication. No food is to be taken until bowels have moved.

*b. By intubation*¹⁶:—Mix 6 gm. of freshly prepared oleoresin of aspidium in 30 c.c. of acacia and 30 c.c. of magnesium sulfate. Pass a Levin tube into the duodenum on an empty stomach. Instill a mixture of 6 gm. of freshly prepared oleoresin of aspidium in 30 c.c. of acacia and 30 c.c. of magnesium sulfate. Withdraw Levin tube, saline purge 2 hours later. Patient should be lying or in sitting position for 2 hours after medication, for fear of mild side reaction of fainting, which occasionally occurs. Treatment with oleoresin of aspidium may be repeated in a week.

5. *Hetrazan*^{15,21,45}:—(50 mg. tablets). Adult—one tablet t.i.d. followed by a purge. One day treatment, may be repeated in a week. Children—Hetrazan (30 mg.) 240 mg. dose each morning for 4 days.

6. *Hexylresorcinol*^{15,21}:—(.2 gm. capsules). No purgative is required before medication. Five capsules are given on an empty stomach. No food for 5 hours. Purge 2 hours after medication. Children up to 6 years—.1 gm. for each year. 6-8 years—.6 gm., and for 8-12 years—.8 gm. Retention enema^{15,46}, buttocks and anus are coated with vaseline and a #22 rubber catheter is introduced for about 15 cm. 400 to 500 c.c. of .2 per cent aqueous solution of hexylresorcinol is instilled. Catheter is left in and open end is clamped. Cheeks of buttocks brought together with tape to help retain fluid for 30 minutes. These enemas should be given on three successive days or at a few day intervals.

7. *Bephenium*¹⁵:—(Alcopar)—Standard dosage regardless of age is 5 gm. of the hydroxynaphthoate which contains 2.5 gm. of bephenium base. The granules are shaken in $\frac{1}{2}$ glass of water and taken orally in single dose in the morning on an empty stomach. No purge is necessary. Foods withheld for a few hours after medication. Dose may be given daily for 7 days.

8. *Piperazine citrate*^{7,11,21,47,48}:—(Antepar). Available in syrup, wafer, and tablet. In pinworm—a single dose of 65 mg./k. not to exceed 2 gm., daily for 8 consecutive days. Since this drug is nontoxic, it may be repeated as often as necessary.

In ascaris no premedication is necessary and no purgation. 75 mg./k. per day not to exceed 3 gm. daily for 6 consecutive days. Daily dose may be divided into two or three portions.

9. *Gentian violet*^{15,47,48}:—(Medicinal) .06 gm. tablets—Contraindicated in alcoholism, cardiac and renal disease.

Pinworm—1 tablet t.i.d. for 19 days.

Strongyloides—1 tablet t.i.d. for 15 days.

Intravenously—.5 per cent aqueous solution 20 mg. i.v. daily for 20 days.

10. *Lêche de Higueron*.—(latex from the fig tree *Ficus Glabrata*). It is not available in the United States but may be obtained from Mexico preserved in a 1 per cent sodium benzoate. This drug is not absorbed and is not irritating to the intestinal mucosa. Being nontoxic, treatment may be repeated, if unsuccessful in the first attempt. The treatment consists of purgation the night before and 60 c.c. of the drug given on an empty stomach the following morning.

11. *Stibophen*^{7,15,21,49,50,51}.—(Fuadin)—2 c.c. I.M. as a test dose. 5 c.c. I.M. every other day until a total of 75 c.c. is given, then 5 c.c. weekly until a total of 100 c.c. has been given. Fuadin is comparatively safe to use and can be given on an ambulatory basis. Should dose cause mild reactions of muscle or joint pain or vomiting, reduce the dose or discontinue treatment for one to two days. Occasional severe reactions may be encountered.

12. *Tartar emetic*^{7,15,21}.—(potassium Antimony Tartare) comes in 5 c.c. ampules of a 2 per cent solution. In the treatment with tartar emetic the patient must be hospitalized. The medication is given intravenously and patient must stay in bed for at least an hour after the intravenous is concluded. If toxic reactions (such as cough, severe headache, muscle or joint pain, vomiting, faintness, or precordial constrictions) appear, treatment must be suspended for a day or two. The dose must be reduced and the intravenous given more slowly. Care must be taken not to allow subcutaneous infiltration, lest painful necrosis occur. Start with 1 c.c. of the 2 per cent solution of tartar emetic in 500 c.c. saline or distilled water intravenously. Increase the amount by 1 c.c. daily until 5 c.c. is reached. Then give 5 c.c. in 500 c.c. saline every other day until a total of 100 c.c. has been given.

13. *Thioxanthone*^{7,8,21}.—(Miracil) in-hospital patients—advantage of use because it can be given orally. Because of its irritating effects on the gastric mucosa is rarely used.

14. *Bal*⁴⁹.—In the use of heavy metals such as arsenic and antimony, when severe toxic reactions occur, the need of a chelating agent is called for.

Bal (dimercaprol) has been found useful in a number of cases. It may be given 2 c.c. of 10 per cent oily solution every 4 hours for 2 days, every 6 hours for 3 days, and every 12 to 24 hours for 7 days (Table II).

SUMMARY

1. The various trials and tribulations in the treatment of intestinal parasites were presented.
2. A discussion of the various drugs used in their treatment was outlined with their advantages and disadvantages.
3. Quick reference tables of drugs of choice, dosage and length of treatment for each parasite are given.

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Clinicopathological Conference*

from the Graduate Hospital of the University of Pennsylvania, Philadelphia, Pa.

Dr. A. Valdes-Dapena (Philadelphia, Pa.)†:—I have a case here of which I have made a fairly detailed abstract. I think you all have it and Dr. Cohn is going to discuss it from a clinical standpoint and give us his impressions of the likely diagnosis. At his request he will receive the radiological opinions whenever he feels that his clinical work-up requires that and Dr. Frobese's surgical judgment will be available for discussion of that aspect of the case.

PROTOCOL

A 64-year old white female was admitted on 6 November 1959 with chief complaint of diarrhea and weakness.

Family history:—The daughter of the patient died of tuberculosis six years before at the age of 30. There was no family history of endocrinopathies, gastrointestinal disorders, arthritis or allergy.

Past medical history:—Appendectomy and removal of one ovary at 24. Thirty years ago (age 34) hospitalized for infection following miscarriage. No history of asthma, rheumatic fever, kidney or skin disorders.

History of present illness:—Ten years ago (1949—age 54) patient began to suffer from arthritis involving mainly the knees, wrists, interphalangeal joints and shoulders. At the beginning arthritic symptoms were rather severe with joint swelling and limitation of function. She was given cortisone over a year's period without much benefit. This therapy was discontinued because of some unknown side-effect. Arthritis has gradually disappeared and during the last year she has not had any joint symptoms.

In March 1959 she noticed rather sudden onset of severe diarrhea consisting of six to ten yellow, foul-smelling, mushy stools not containing blood or other pathologic products. With the onset of diarrhea she began to feel extremely weak, anorexic and she suffered a loss of 20 pounds in weight over a period of four months. There was no abdominal pain, nausea or vomiting. About June of 1959 she began to have a nonproductive persistent cough with no hemoptysis or chest pain.

She was then admitted to another hospital where she was found to be anemic and dehydrated. No definitive diagnosis was made. Following discharge

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she did fairly well for several weeks and gained some weight. She had to be readmitted on 20 October because of recurrence of severe watery diarrhea, weakness and weight loss.

During the few weeks preceding her next admission at this hospital the diarrhea had subsided somewhat. She was having two or three large, very soft stools usually in the morning. The patient was anorexic, weak and short of breath on exertion.

Physical examination:—Blood pressure 92/44; respiration 16; pulse 68.

Pale, malnourished, chronically ill female who appeared very lethargic. Nontender, freely movable lymph nodes present in the cervical area, axillae and inguinal region. Chest clear. Heart slightly enlarged with a grade 2 basal systolic murmur.

Abdomen:—Protuberant, soft and tympanitic with no areas of tenderness. No evidence of fluid, enlarged organs or masses. Rectal examination negative.

Extremities:—No edema. Joints functioning well with only minimal deformity. Skin very dry with many excoriated and ecchymotic areas over the trunk and anterior surfaces of the extremities.

Course:—Following admission the clinical condition of the patient rapidly deteriorated. She became febrile, dyspneic, cyanotic and extremely weak, with more marked diarrhea and a high leucocytic response. In view of the life-threatening situation, the patient was started on a program of antibiotics, careful blood replacement and steroids parenterally (200 mg. Solucortef daily). Under this program she showed a slow improvement. Five days following admission Isoniazid in a dose of 400 mg. was added to the program. After a week the patient was afebrile and more alert. At this point oral steroid therapy with 15 mg. of prednisone, three times a day, was started. A week and a half after admission studies were interrupted because, as a result of a fall, the patient suffered a fracture of the right femur and a probable skull fracture. X-rays failed to confirm the diagnosis of skull fracture. ENT consultation at this time uncovered a perforation of an ear drum with watery discharge.

There had been no loss of consciousness following the fall but in the succeeding days the patient developed convulsions. Her general condition worsened. On 2 December bilateral frontal burr holes and temporal burr holes were done. A xanthochromic fluid was obtained. The patient became more alert. On 8 December she complained of generalized abdominal pain and the abdomen was somewhat distended. Steroid therapy had been reinstituted together with molar lactate, antibiotics and oxygen. Some slight improvement ensued. For the first time abundant tarry stools appeared. The dosage of steroids was reduced. On 11 December stools were yellow again. On the following day she was found dead in bed by the nurse.

Laboratory Data:—**Glucose Tolerance Test**

FBS	131
% hr.	65
1 hr.	140
2 hrs.	155
3 hrs.	166
4 hrs.	110
5 hrs.	56
6 hrs.	48

Urines Negative

Shilling Test—% excretion—24 hr. urine volume of only 260 c.c.

¹³¹I triolein (11/9/59)—specimen of stool probably contaminated with urine

Blood levels 2 hrs. 1.6%

4 hrs. 3.2%

Fecal excretion (506 days)—31.0%

¹³¹I triolein (repeat study)—patient on steroids

Blood levels 2 hrs. 5.3%

4 hrs. 10.4%

6 hrs. 11.4%

8 hrs. 11.2%

24 hrs. 4.1%

Fecal excretion 3%

	11/7/59	11/9/59	11/13/59	11/27/59
Hb	8.7	8.0	10.4	11.4
WBC	10,500	33,800	12,400	18,800
N	86	94	88	84
L	13	4	11	15
M	1	2	1	1
Platelets	234,000			
Prothrombin	100%			
ESR	34			
HT	31			
FBS	110			121
BUN	21			45
CO ₂	24		29	22
Cl	101		108	102
Na	122	123	144	137
K	4.7	3.5	4.7	5.0
Ca	8.4	9.2		
Phosphorus	3.66	6.30		
Amylase	130			
Lipase	0.52			
Cholesterol	105	60		
Esters	100	35		
Bilirubin direct	.07			
total	.82			
PBI	1.8 mcg.			
17 Ketosteroids	8.2 mg.		.118	
LAP	1,280 c.c.			
Urinalysis				
S.G.	1.020			1.007
Alb.	faint trace			faint trace
Microscopic	Neg.			35-75 WBC
PPD #2	plus 2	plus 3		2-3 RBC
Histoplasmin	Neg.			

SPEPP	8/3/59	11/17/59
Alb.	2.37 gm.	2.57 gm.
Alpha 1	.34 gm.	.48 gm.
Alpha 2	.54 gm.	.85 gm.
Beta	.68 gm.	1.01 gm.
Gamma	2.17 gm.	1.93 gm.
Total protein	6.1 gm.	6.9 gm.
Peripheral smear—normochromic		
Normocytic anemia		
Bone marrow—not diagnostic		

*Dr. Edwin M. Cohn (Philadelphia, Pa.)**:—I'm sure by this time all of you have had an opportunity of reading through this protocol and so to save time, let me review some of the features which I feel are more pertinent to our problem.

The patient is a 64-year old white female whose primary complaint was diarrhea and weakness. There was a family history of tuberculosis. Ten years prior to the onset of her current complaints, this woman had symptoms compatible with a diagnosis of arthritis. Despite therapy there was no apparent improvement, but eventually the arthritis seemed to have improved or at least abated spontaneously, shortly prior to the onset of her current complaints.

The diarrhea was profuse, foul-smelling, watery; it did not contain blood; no mention is made of the associated symptoms of pain.

Apparently those complaints went on for a rather prolonged period of time and one has the impression that although an attempt was made at therapy, it was not convincingly effective. With the passage of time the majority of her complaints seemed to have disappeared, perhaps spontaneously. Remission was followed by return of symptoms. Consequently, there was no direct correlation between the therapy and improvement; neither was there obvious modality that might have aided in provoking a recurrence.

Of the physical findings, the woman unquestionably was ill, showing evidence of anemia, and of malnutrition. There was a basal systolic murmur. Except for a rather protuberant and tympanitic but soft abdomen there were no other significant positive findings.

Her course was such that after being placed on a program that consisted of antibiotics, blood replacement, and steroids, she slowly improved.

Another therapeutic agent was the Isoniazid, and after one week of this medication, the patient was afebrile and more alert. Whether the patient had started to improve at that point or began to show improvement after the Isoniazid was given is a point for consideration.

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At this time the patient suffered an accident, a fracture of the leg, and evidence of cerebral bleeding which was relieved surgically. Steroid therapy was re-instituted in an effort to handle the recurrence of her primary and original complaints. A complication ensued in the form of a tarry stool. Shortly after stool returned to a normal brown color, a rather unexpected and sudden demise occurred.

I'd like to point out some of the helpful laboratory studies.

I think it is of significance to know that the fasting blood sugar taken during the course of a glucose tolerance test was 131 mg. per cent, which is above what is generally considered to be top level of normal.

I might point out, also, that the actual peak of the curve did not occur until three hours.

Insofar as the triolein study was concerned, this was considered to have been normal as a study for intestinal absorption.

The hemoglobin depression, the leucocytosis, the elevated poly count were rather consistent. There was an elevation of her sedimentation rate.

Towards the end of her illness there was evidence of renal damage, manifesting itself both by pyuria and an elevation of BUN.

I think it's rather important, also, to point out the unusually low level of blood cholesterol which on one occasion was 105 and esters 100 mg. per cent and when repeated was even lower at 60 and 35 mg. per cent, respectively.

Other studies, of course, were carried out, but I would like to point out the plus two and plus three reaction of the PPD.

So far as the electrophoretic pattern is concerned, it is generally conceded to be more helpful when the diagrammatic representation is present, but on the basis of the figures that have been presented, there was evidence of hypergammaglobulinemia.

In summary then, a 64-year old woman with a previous family history of tuberculosis who was admitted to the hospital because of profuse diarrhea, anorexia, weight loss, weakness, anemia, who had spontaneous subsidence of symptoms, and recurrence for no apparent reason, but who showed on other occasions some indication of improvement in the course of her illness following certain therapeutic agents, such as, steroids, blood replacement, and antibiotics. The problem apparently resolves itself around symptoms of diarrhea, anorexia, weight loss, profound weakness, anemia, leucocytosis. The various possibilities which would include these symptoms in a woman of this age make it necessary to consider malignancy of the intestinal tract.

I think there is, however, one feature in her illness which would have a tendency to negate this as a consideration and that is to be found in the periods

of improvement in which there was a spontaneous disappearance of her diarrhea, an increased sense of well-being, weight gain, and increased appetite. Regional enteritis might provide the same type of picture. Once, however, the severity of symptoms in regional enteritis present to such a degree, it is unlikely for improvement to occur spontaneously.

I think we can at the same time rule out infectious diarrhea because of the spontaneous remissions and exacerbations and the duration of the complaints.

One must, of course, consider tuberculosis, involving either the small bowel and/or the large bowel. On the basis of the information that is provided to us, antituberculosis treatment was instituted, and there was no significant improvement. One can gather, also, that the clinicians apparently were not impressed with great conviction that this was a primary diagnosis since this type of therapy had not been instituted earlier. True, there was a positive reaction to a PPD test, but this has to be interpreted without benefit of other evidence of tuberculosis and without certain x-ray studies of which a film of the chest is important.

A malabsorption syndrome can be ruled out by the peaked glucose tolerance curve and normal triolein study.

There is a clinical entity which incorporates many of the reported findings. This is a clinical entity that includes the arthritic manifestations which precede gastrointestinal symptoms; a clinical entity that shows evidence of a general systemic nature where synovial membranes, the endocardium, and the gastrointestinal tract are involved. The diagnosis of this many-faceted type of illness which has been considered to be allied to the collagen diseases, may well be represented by Whipple's disease. There are certain other features which may support that very diagnosis. Whipple's disease involves lipid metabolism and during the course of this illness, there has been interference with lipid metabolism.

It would be interesting, however, to interpret the episode of bleeding that occurred in the terminal stages of her disease. It may well have represented a complication of steroid therapy; it could have represented, also, a secondary manifestation of the cerebral trauma; it may have been bleeding complicating small bowel disease.

I think the cause of her demise is one of true speculation. It could have complicated her neurological problem; it may have been a recurrence of the bleeding; it may have represented some abdominal catastrophe.

Between the potential diagnosis of tuberculosis involving the small and/or large bowel or Whipple's disease, I would favor Whipple's disease as a diagnosis on clinical grounds for this patient.

I think perhaps we can have many of our questions clarified by presentation of x-ray films.

Dr. George N. Stein (Philadelphia, Pa.):—The x-rays which have been selected to be shown this afternoon for this case are those which we think show most of the findings that will either help make the diagnosis or eliminate some of the possibilities.

The chest x-ray did not show any evidence of tuberculosis. It is possible, of course, to have gastrointestinal tuberculosis without having pulmonary tuberculosis.

In the film of the abdomen and part of an intravenous urographic study I think you can see the arrows which indicate two annular, rather large calcifications. These are in the location of the adrenals in this projection; the one on the left side is rather characteristic of a splenic artery aneurysm; the one on the right should be characteristic of an aneurysm and I presume it is the hepatic artery, because in the lateral view

(Slide) you can see that it is anterior and is not located in the region of the adrenal so that I would favor these representing aneurysms, one of the splenic artery and one possibly of the hepatic artery.

(Slide) This is part of a small intestinal study; there is coarsening of the mucosal pattern in the jejunum and segmentation of the barium which I think shows a little better in the next film. There is also coarsening of the mucosal pattern in the ileum.

(Slide) This is also part of the same examination which again shows the clumping or segmentation of the barium. There is nothing here to suggest regional enteritis, particularly of the stenosing variety; the process is entirely too extensive, I think, for nonstenosing regional enteritis.

It is the pattern that has characteristically been spoken of as the "nutritional deficiency pattern", the pattern that is associated with idiopathic steatorrhea.

In Whipple's disease, which Dr. Cohn has mentioned, a similar type of pattern is encountered. The differences between the configuration seen in Whipple's disease and that seen in idiopathic steatorrhea consists of two major points. In idiopathic steatorrhea the intestine frequently is dilated. I think that loops such as this one are probably slightly dilated; in Whipple's disease there is no dilatation of the intestine. The other difference is that in idiopathic steatorrhea the moulage sign, the formless appearance of barium in some of the loops, is encountered and this is not seen in Whipple's disease.

Also in Whipple's disease the transit time is not affected significantly; in idiopathic steatorrhea there is frequently a great deal of hypomotility.

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So that on the basis of the roentgen studies alone we would have to consider both of those possibilities.

Tuberculosis, particularly peritoneal tuberculosis can cause a pattern similar to this as can peritoneal carcinomatosis.

Lymphosarcoma of the small intestine does not look like this; usually the loops are separated from each other due to the infiltration of the lymphoma in the mesentery.

So that from the roentgen standpoint we would be concerned with carcinomatosis of the peritoneum, tuberculosis of the peritoneum or either idiopathic nontropical sprue steatorrhea or Whipple's disease.

The possibility of a collagen disease such as scleroderma which can involve the small intestine seems unlikely since this is not the pattern usually associated with it and since intestinal involvement with scleroderma usually does not occur in the absence of esophageal involvement which we could not recognize in this patient.

So that we would favor the possibility of Whipple's disease or nontropical sprue as the cause for these findings, both clinically and radiographically.

Dr. Valdes-Dapena:—We have a surgeon on the panel who is from our hospital, and I would like to ask his opinion because in abdominal problems I have always found out that surgeons have a great deal of accuracy in their diagnosis. I think it's because they have the advantage over clinicians that they so frequently check on themselves by going in and looking.

I wonder what Dr. Frobese's impression has been when he read this over, what diagnosis he would favor and whether he would operate.

Dr. Alfred S. Frobese (Philadelphia, Pa.):—I'm glad you put that last statement in because you made it a lot easier for me to talk now.

Certainly, in reading over this protocol, I did not come to any other ideas than did Dr. Cohn. I think it's only fair to say I certainly did not come up with the idea of Whipple's disease, never paying much attention to such lesions as that. I did give some thought to the possibility of regional enteritis, although I discarded it for the same reasons that he did; and furthermore having seen the x-rays I certainly would discard that diagnosis.

Even if this is a case of regional enteritis it certainly would not be one in which I would feel surgery was indicated. Our concepts in this regard today are that regional enteritis is not managed surgically unless it is complicated by obstruction or one of the inflammatory lesions such as fistula or abscess formation and some of the other complications of that lesion.

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Tuberculosis, certainly I had discarded for the number of reasons that he had.

One thing did interest me a little bit though; and that was the possibility of tuberculous peritonitis. This I think I would discard again (even though she has positive PPD's) in the absence of any findings in the chest for it would seem to me that this is a bit far afield.

The other possibility that's been mentioned is carcinomatosis of the peritoneum. But something interests me about this and that was the inflammatory lesion with which this woman presented at the hospital. I would be rather surprised to find carcinomatosis of the peritoneum causing a febrile state and with such marked leucocyte response and such a marked shift to the left for the leucocytes toward the polymorphonuclear area. I wonder if enough attention has been given to the possibility of a peritonitis based on suppuration or inflammation.

Whenever I think of undiagnosed peritoneal inflammation I can't help but think of the possibility in this age group of unrecognized appendicitis; every year it seems to me we are surprised by this. In the elderly patient who presents with an acute or smoldering condition in the peritoneum which seems somewhat obscure, it turns out that the process originated with an appendicitis which perforated.

We really do not have any objective evidence of that. Perhaps in going over the abdomen one might have been able to determine whether something on the order of peritoneal irritation was present, but I cannot tell that from reading this protocol.

I would like to say just a word about the second question Dr. Dapena posed and that is whether or not surgery might be indicated.

If I saw this woman I might think of it rather seriously because it seemed to me that having seen that chest film and going on the basis of her story before, something was going on in this abdomen which was rather serious in nature and it might have been the wise idea, I think, early in the course to consider exploration.

If the nature of her peritoneal problems were inflammatory, a good deal could have been accomplished and it is possible that even if this were due to tuberculous peritonitis something could be accomplished by laparotomy. Obviously if it were a neoplasm this extensive in nature very little could be accomplished.

Aside from that I would like to mention the point that Dr. Stein has brought up in regard to the splenic arterial aneurysm and possibly the hepatic arterial aneurysm. The question, of course, must come to mind now as to whether or not that might have had something to do with her sudden demise.

Splenic artery aneurysms have received much attention in the surgical literature lately, particularly since we've been looking for new horizons in vascular surgery and as more advances are made we look for areas to deal with. A number of surgeons have been suggesting that splenic arterial aneurysms are very prone to rupture, particularly in the face of associated severe disease or disorders and associated pregnancy, and that finding such a lesion constitutes just cause for resection of the spleen and the aneurysm.

I personally have never seen a splenic arterial aneurysm that ruptured and I have the impression, Dr. Stein may bear me out or perhaps he won't, that we see a number of these in the ordinary roentgen films of the abdomen.

It would seem to me that perhaps Dr. Dapena ought to see more of these ruptures if they are quite common. I do not believe I would have recommended that this splenic arterial aneurysm be approached surgically in this particular phase in her clinical course, but I do think that one might give some thought to it being the cause of her sudden demise.

Dr. Valdes-Dapena:—There is only one comment that I would make from the clinical side, if I am allowed and that is that tuberculosis of the gastrointestinal tract would have been very surprising to me in a case without pulmonary lesions. We studied a series of 200 cases of fatal tuberculosis at Philadelphia General Hospital. Important lesions were only found in these cases. In the rest of our autopsy material we found five instances of intestinal tuberculosis without pulmonary tuberculosis of an active type, but they were always small lesions; there were isolated ulcers or scars that might have produced a stricture. So that diagnosis I would not have accepted too readily.

This case was presented as a test to a group of graduate students and because of the family history, that diagnosis was held by a couple of them; they also were strong for carcinomatosis; for malabsorption syndrome without naming a particular cause including the possibility of Hodgkin's that might produce lymphatic obstruction. One of them maintained the diagnosis of Whipple's disease throughout.

I'm now going to show you the pathology. First I am going to show you something that I have to beg your indulgence for withholding from the protocol. It was a small bowel biopsy.

Nowadays if we had to just restrict ourselves to the cases that have no pathologic material at any time before the autopsy we would have no cases. With tubes and needles and smears they always manage to get tissue from some place and there is usually something morphological to show.

Question:—During this period was sarcoid mentioned?

Dr. Valdes-Dapena:—No, sarcoid was not mentioned.

Question:—Was a lymph gland biopsy done?

Dr. Valdes-Dapena:—That was done in another hospital. They did liver biopsy and lymph node biopsies in another hospital and they gave us no diagnosis.

(Slide) This is the slide of the small bowel biopsy which presents the features that you see here. Predominantly this increase in the volume of *lamina propria* that you see is disproportionate to the glands. There is a light-staining quality throughout due to the fact that there are a great many cells in the *lamina propria* that have a small nucleus and an abundant and very light-staining cytoplasm.

There is also this feature: There are several microcystic spaces in the *lamina propria*.

I had never seen a case of Whipple's disease. Accustomed as we are to being very objective about everything I was beginning to think that Whipple made the whole thing up. When I saw this it was something that immediately struck me because you don't see this in any other condition.

(Slide) Then a periodic acid Schiff stain was done and all those cells stained a very deep red, so deep that even the positive reaction that you get normally from mucin with that stain seems pale by comparison. There is probably nothing that you can name that will give you such an intensely positive periodic acid Schiff reaction as these cells in Whipple's disease.

So actually a few days before the final turn for the worse the diagnosis was established on the basis of a very good sample of small intestinal mucosa taken through a tube.

(Slide) The autopsy material was, as expected, very striking. This is a view of the small bowel and you see the large lymph nodes and the lymphatics that are stuffed full of material that looks yellowish. This appearance, which has been compared to the wax drippings from candles, is characteristic of Whipple's disease. The entire small intestine was involved; also the colon was involved; the stomach did not appear particularly abnormal.

(Slide) This is a closer view of that area that a surgeon, for instance, would have considered typical of Whipple's disease.

(Slide) The mucosa throughout was abnormal. In the cecum and in most of the large bowel there were actual nodules which represented accumulations of those same cells combined with a certain amount of retained fat. By this time we have seen the cysts that represent fatty deposits as well as the PAS positive cells which contain the specific material which is not a fat.

(Slide) This is a close-up view of the bowel mucosa with flecks and spots and nodules of this yellowish material.

(Slide) The lymph node has been described as being a very telling element in the gross diagnosis of the disease. They have described it as having a spongy

texture and the appearance of it is suggestive of the presence of small soft areas in it. It is like tapioca and this node from the autopsy was very characteristic of that type of change.

(Slide) Under the microscope what you see in the lymph node is the accumulation of cells similar to the ones in the *lamina propria*.

(Slide) Now here you can see better that those red things are actually particles. Ordinarily we refer to these cells as sickleform-particle-containing cells, often abbreviated as SPC cells. These positive particles do have, when examined under high magnification, resemble not so much a sickle as the sickle cells of sickle-cell anemia. In this case they were easily recognized.

(Slide) The liver as well as the spleen, and all the organs of the abdomen, were covered by a thickened serosa. There was in this case a polyserositis; there were adhesive pericarditis, pleuritis, pleural adhesions, no fluid and a granular appearing peritoneum.

(Slide) In the liver in this disease sometimes you may find massive deposits of those cells in the portal spaces. In this case there was very little and it would be excusable that the diagnosis was not made on liver biopsy elsewhere.

(Slide) In the lungs, in the alveoli there were accumulations of these cells. This is a PAS stain and you see how dark red they stain; the possibility, of course, has been mentioned of making the diagnosis of Whipple's disease by doing a periodic acid-Schiff stain on sputum.

(Slide) Now this patient had a very distinctive endocarditis involving the aortic valve. These wart-like excrescences on the cusps of the aortic valve are not like those of subacute bacterial endocarditis; they look something like the *lupus* lesion, the Libman-Sacks endocarditis; they are pale and they are very firm; they have a very decidedly coherent texture; you cannot break them off easily.

(Slide) Microscopically what we find in those warts and rugae of the cusps is largely an amorphous hyalin material with collections, streaks of PAS positive cells.

(Slide) This is the spleen covered with the same type of very thick serosa.

(Slide) Within this spleen there was not a great deal of the type of material we have been talking about, but around the arteries you could find cells like that.

(Slide) In the bladder which grossly had not any particular appearance, these cells were present; not many, but distinctive.

(Slide) In the loose connective tissue that we have picked up in various places of the body the positive material was demonstrated also.

(Slide) This is a high magnification to show you the shape of these particles which varies from an actual sickle-like form to a long filament just like the cells of sickle-cell anemia. Of course these are very minute.

(Slide) The final episode was a hemorrhage which seems to have recurred because it subsided clinically and at autopsy it was massive. The entire gastrointestinal tract was filled with recently shed blood due to an ulcer in the duodenum. There were also smaller ones. The pattern is very much like the Cushing's or Curling's ulcers produced by stress. There is the one aneurysm of the splenic artery that was demonstrated. The other one I could not find.

(Slide) Here the aneurysm is open; it's a fairly large one for the splenic artery.

(Slide) And here is the point of bleeding within the ulcer. You see that this is a diffuse necrosis. This does not look like a chronic peptic ulcer. In the center a fairly large artery was eroded.

I am very happy that Dr. Cohn made the diagnosis and that Dr. Frobese did not have to operate. I think they considered it.

Dr. Frobese:—This is another example of the medical man trying to put the surgeon out of business. The small intestinal biopsy, I see, is going to really hurt us in the end.

(Laughter.)

NEWS NOTES

1961 AMES AWARDS

The American College of Gastroenterology, in cooperation with Ames Company, Inc. of Elkhart, Ind., presented its 1961 Ames Awards at the Annual Banquet held at the Sheraton-Cleveland on Tuesday evening, 24 October 1961.

These awards are given annually for the best papers published in the official publication of the College, *THE AMERICAN JOURNAL OF GASTROENTEROLOGY*.

First prize and certificates went to Drs. Louis M. Rousselot, William F. Panke, and Augusto H. Moreno of New York, N. Y., for their paper "Further Evaluation of Splenic Pulp Manometry as a Differential Diagnostic Test of Acute Upper Gastrointestinal Bleeding".

The second prize and certificates were awarded to Drs. Eric E. Wollaeger, and Paul A. Green of Rochester, Minn., for "Idiopathic Nontropical Sprue (Malabsorption Syndrome)".

The third prize and certificates were given to Drs. David G. Pietz, B. D. Rosenak, and R. N. Harger of Bluffton, Ind., for "Alcohol Metabolism in Hepatic Dysfunction".

The presentation of the awards was made by Dr. Hugh A. Miller, Assistant Medical Director of Ames Company.

In Memoriam

We record with profound sorrow the passing of Dr. Cyril E. Savage, Lima, Ohio, Fellow of the American College of Gastroenterology. We extend our deepest sympathy to the bereaved family.

ABSTRACTS FOR GASTROENTEROLOGISTS

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ESOPHAGUS

THE INTERRELATION OF PULMONARY AND ESOPHAGEAL DISEASE: Arthur M. Olsen. *J. Internat. Coll. Surgeons* 33:12 (Jan.), 1960.

Because of the close relation between the esophagus and the respiratory tract, disorders of deglutition are likely to have serious effects on the bronchi and lungs. Less frequently, disorders of the esophagus are caused by diseases of the respiratory tract. Of greatest importance are those disorders which are responsible for the "failure to open" of either the upper or the lower sphincter of the esophagus. Disturbances of the central nervous system, muscular weakness syndromes and achalasia of the cardia

are the chief causes of aspiration pneumonia. The degree of retention and the lack of esophageal peristalsis probably are the factors of chief importance here. Intubation and gastrostomy often are necessary when the function of the cricoid sphincter is disturbed, and tracheotomy may be life-saving in such cases. Relief of obstruction of the esophagus or at the cardia is essential to the treatment and to prevention of pulmonary complications.

GLENN S. ROST

ESOPHAGEAL AND ANTRAL STRICTURES DUE TO INGESTION OF HOUSEHOLD AMMONIA: REPORT OF TWO CASES. Richard A. Norton. *New England J. Med.* 262:10 (7 Jan.), 1960.

Two cases of ingestion of household ammonia were presented. The initial result was the development of burns of the mouth and upper digestive tract and a sterile pneumonia with pleural effusion. After several weeks, esophageal and antral strictures developed in both patients which required by-passing surgery.

A review of the literature of this subject is made as well as comments as to the locations of damage in the gastrointestinal tract

associated with the ingestion of different corrosive chemicals. It was stressed that the effects on the gastrointestinal tract after the ingestion of ammonia were similar to that of lye.

Therapy consists of the avoidance of gastric lavage or emetics, early x-ray study and esophagoscopy and, if burns are found, then early bougienage. The use of steroids should be considered when burns are severe.

MORTON SCHWARTZ

ESOPHAGEAL CYSTS: Gerard Desforages and John W. Strieder. *New England J. Med.* 262:60 (14 Jan.), 1960.

Three cases of esophageal cyst are presented. In the first a small intramural cyst

was discovered incidental to exploratory thoracotomy for a suspected coin lesion in a

24-year old man. In the second case complete obstruction to swallowing appeared suddenly in a 32-year old man. Esophagoscopy was negative but x-ray of the esophagus disclosed a cyst-like structure. A 2.5 cm. long cyst was enucleated from beneath the muscular coat of the esophagus at a level just below the carina. The pathological report was "bronchial-cleft cyst lined by squamous and respiratory epithelium" in the first case and "benign embryonic structure apparently of respiratory-tract origin" in the second. The third case was that of a

20-year old woman who developed sudden hemothorax secondary to a bronchogenic esophageal cyst. Although gastric epithelium was not reported peptic ulceration and perforation is offered as the explanation of events.

The embryological theories of development of esophageal cysts are reviewed. In view of the likelihood that these cysts arise as a result of accessory buds pinched off from the primitive foregut the authors suggest the term "primitive foregut cyst".

ERNEST LEHMAN

STOMACH

NEWER CONCEPTS IN THE MEDICAL TREATMENT OF DUODENAL ULCER: C. Joseph DeLor. Wisconsin M. J. 58:695 (Dec.), 1959.

The author presents a very concise summary of the causes of increased gastric secretion in duodenal ulcer. The significance of heredity, stress, habits, drugs, endocrine disturbances, burns, intracranial lesions, and

foods are considered. Hypersecretion is considered the most consistent finding in duodenal ulcer and medical treatment directed to reducing this secretion is outlined.

BERNARD FARFEL

SOME CHARACTERISTIC PATTERNS OF THE ELECTROGASTROGRAM IN LESIONS OF THE SMALL INTESTINE: H. S. Morton and J. F. Davis. Canad. M. A. J. 81:1000 (15 Dec.), 1959.

An electrogastrogram placed in the stomach records muscular and glandular activity not only of that area but also of the small intestine. Malignant disease interferes with the regular contractions of the bowel wall and an irregular pattern results. Several cases are presented in which such a pattern was obtained and the presence of a gastrointestinal malignancy was confirmed at surgery.

Some normal individuals with dyspepsia had more than average activity as manifested by their history, borborygmi heard, the number of bowel movements per day and greater than normal activity on the electrogastrograms. This activity was re-

duced by bed rest, admission to the hospital, anticholinergic drugs and vagotomy.

After studying a group of individuals with regional enteritis and ulcerative colitis the authors concluded that the vagotomy is a very beneficial procedure as measured by the electrogastrogram before and after surgery.

Two situations which apparently are not benefited by vagotomy are those patients with regional enteritis who have an irreversible inflammatory process with fibrosis and patients with ulcerative colitis in the distal half of the colon.

THEODORE COHEN

GASTROINTESTINAL CANCER: Jeanne C. Bateman. Am. J. Proct. 10:415 (Dec.), 1959.

This is an interesting report of the use of adjunctive chemotherapy in the treatment of gastrointestinal cancer.

The author presents a series of 66 patients with this disease in which Thiotepe was used intravenously, orally, intracavitary

and intratumor. Their results were then compared as to survival periods with the survival periods in Connecticut, as reported by the Connecticut Board of Health in 1955.

The author concludes that continuous

treatment with Thiotepa from the time of surgery in patients with gastrointestinal carcinoma is worthwhile and their results demonstrate a 40 to 75 per cent improve-

ment in survival rates over those patients in the Connecticut series treated without Thiotepa.

PAUL LEDBETTER

CANCER OF THE STOMACH: Milton F. Bryant and William D. Lazenby. J. M. A. Georgia 48:597 (Dec.), 1959.

More than 40,000 persons die annually in the United States from cancer of the stomach. During the eight-year period, 1948-1955, 129 patients with carcinoma of the stomach were seen at Grady Memorial Hospital. The most common presenting symptoms were weight loss, 85 per cent, and epigastric discomfort, 58 per cent. The average duration of symptoms before diagnosis of the lesion was 7½ months.

It is necessary to consider gastric cancer in all patients who have unexplained and

persistent digestive complaints. Carcinoma of the stomach is a curable disease, notwithstanding the gloom and discouragement that are usually associated with statistical studies.

This paper again emphasizes the fact that anyone over 40 years of age with weight loss and gastric symptoms must be considered having a possible gastric malignancy.

I. HENRY EINSEL

STUDIES ON ROBUDEN, EXTRACT FROM STOMACH AND DUODENUM; ITS EFFECTS UPON GASTRIC SECRETION AND CLINICAL COURSE OF PEPTIC ULCER: George B. Jerzy Glass and Saul A. Schwartz. Am. J. Digest. Dis. 4:988-1013 (Dec.), 1959.

The subject has been with us for 35 years and, except for the enterogastrone and urogastrone era, has occupied the minds of foreign medical men more than of our own. Also the majority of publications deal with this product's effects upon the clinical course of peptic ulcer which makes the authors' paper all the more important to anyone wishing to see laboratory data instead of statistics based on less dependable factors as x-ray or patients' reports. The paper deals with subjects like electropho-

retic pattern; carbohydrate spectrum; intrinsic factor and peptic activity of the substance. The report then turns to the effect of Robuden on the secretory output of hydrochloric acid; pepsin; and mucous substances in the stomach as well as with the effect of Robuden upon peptic activity *in vitro*. The final chapter falls into the above mentioned category of judging clinical effectiveness.

WALTER CANE

STRESS ULCERS IN THE STOMACH: I. M. Breckenridge, E. W. Walton and W. F. Walker. Brit. M. J. 5163:1362 (19 Dec.), 1959.

Stress ulcers of the stomach are acute peptic ulcerations or multiple hemorrhagic erosions appearing after various forms of stress in the absence of any chronic ulcer disease. Curling's ulcer and Cushing's ulcer are produced by stress. Similar ulcers have been observed after various injuries, infections and operations. Six cases of acute peptic ulceration are described, five with severe gastrointestinal hemorrhage and one with extensive perforation occurring a few days after cerebral hemorrhage, acute encephalomyelitis, fracture of the hip, and

operations for cancer of the bladder and the uterus. Disease or injury of any part of the brain may produce adrenal cortical stimulation that leads to gastric ulceration. Similar ulcers after trauma, infection or surgery may be due to embolism with fat, tumor particles or necrotic materials. This form of ulcer seems to be associated with gastric hyperacidity just as a chronic peptic ulceration, therefore prophylactic antacid therapy is advisable.

H. B. EISENSTADT

POSTGASTRECTOMY ANEMIAS: Stanley A. Fruchtman. *J. Lancet* 79:55 (2 Dec.), 1959.

Postgastrectomy anemias are common and oftentimes very marked. The anemia may be either iron-deficiency or rarely megaloblastic in character. The author gives a very valuable resumé of iron metabolism in the human body and points out the reasons for postgastrectomy anemias. Iron deficiency anemia is most marked in the Billroth II type procedure, in which food stuff is made to by-pass the entire duodenum and proximal jejunum, where most of the iron absorption takes place. Megaloblastic anemia

is not common as an immediate result of gastrectomies, but is increased with increasing postsurgical longevity. When present, it is indistinguishable from pernicious anemia. It is most commonly found in total gastrectomies, and is probably due to malnutrition resulting therefrom. Iron deficiency anemias will respond to oral and in some cases parenteral administration of iron. Megaloblastic anemia responds well to parenteral Vitamin B₁₂ administration.

A. J. BRENNER

LEIOMYOSARCOMA OF THE STOMACH PRESENTING AS AN ACUTE ABDOMEN: James R. Webster, Jr. and John J. Bergan. *Quart. Bull. Northwestern Univ. M. School* 33:343 (Winter), 1959.

Gastric leiomyosarcoma is a relatively rare malignancy. Only 180 cases have been reported. They may grow to considerable size and still be curable by surgical excision. Five-year survival rates of 54 per cent have been reported, and a 6-year survival after metastasis. The three usual clinical features are: gastrointestinal bleeding, epigastric distress, and a palpable mass in the epigastrium. Necrosis commonly occurs. Unlike lymphosarcomas they are unresponsive to radiation.

A case of a 49-year old negro female is reported. She complained of severe abdominal pain. Tenderness and guarding masked a 6 by 8 cm. mass until pain subsided on the second day. The sedimentation rate was 40; x-ray showed a defect on the greater curvature of the stomach characteristic of extrinsic pressure. At operation the mass lay in the gastrocolic mesentery attached to the greater curvature of the stomach.

ERNEST LEHMAN

ADULT PYLORIC OBSTRUCTION DUE TO A MUCOSAL DIAPHRAGM: Digby Chamberlain and N. V. Addison. *Brit. M. J.* 5163:1381 (19 Dec.), 1959.

There is a large number of intrinsic diseases of the stomach that can cause pyloric obstruction; for instance, peptic ulcers, benign or malignant tumors, specific and nonspecific granulomas, spasm and foreign bodies. One of the rarest causes of obstruction is prepyloric or pyloric mucosal diaphragm. This abnormality which is probably congenital is not demonstrable by clinical, laboratory, or x-ray methods and even by surgical exploration unless the stomach is opened. Two cases are reported with the history of postprandial fullness, gaseous eructations and vomiting after meals, show-

ing gastric dilatation and nonspecific pyloric narrowing during x-ray examination. The diagnosis was not established until a careful inspection of the surgical specimen was made after partial gastrectomy. It revealed a mucosal diaphragm just before or inside the pylons covered with gastric mucosa on one side and duodenal mucosa on the other. Differential diagnosis must include congenital or acquired idiopathic hypertrophy of the pylorus, chronic hypertrophic antral gastritis and prolapse of the gastric mucosa into the duodenum.

H. B. EISENSTADT

PROBLEMS FOR THE RADIOLOGIST IN DIAGNOSIS OF GASTRIC ULCER: W. G. Scott, B. S. Loitman and H. A. Swanson. *J.A.M.A.* 171:2048 (12 Dec.), 1959.

The authors describe their x-ray technic for the examination of the stomach. There are no absolute criteria for the diagnosis

of malignancy in ulcers. They consider the benign criteria to be the following: 1. Protrusion of the ulcer crater beyond the

stomach wall, with a smooth floor and contour. 2. Demonstration of mucosal folds radiating into the ulcer crater. 3. Demonstration of a narrow band of translucency about the neck of the crater formed by a collar of overhanging mucosal edges (Hampton's lines). 4. Absence of induration around the base of the ulcer with pliable adjacent stomach wall and persistence of peristaltic movement through the area of ulceration. Usually two or more of these characteristics form the basis for this diagnosis. With these criteria, the diagnosis of malignancy in a benign appearing ulcer will be missed by a skillful roentgenologist in as high as 6 per cent of cases; but the mortality from operation will be at least

this high. For this reason the authors recommend a medical regimen for two or three weeks, with re-examination at the end of this period. If the lesion is definitely smaller, the medical treatment is continued for another three- or four-week period. It is desirable to repeat the examinations a third time to be certain that complete healing has occurred; if it has not, surgical treatment is indicated. Since patients with histamine-fast achlorhydria and recurrent gastric ulcers are more prone to malignancy, the above criteria are made more stringent for these types of patients. The authors also state that there is a 20 per cent error in over-diagnosing malignancy in gastric ulcer.

S. L. IMMERMAN

INTESTINES

DIETARY MANAGEMENT IN LOWER GASTROINTESTINAL DISEASE: Duane Smith. *J. Lancet* 79:454 (Oct.), 1959.

This is a brief review of dietary management of some gastrointestinal diseases. The basis for use of a gluten-free diet in idiopathic steatorrhea is discussed and the necessity for eliminating wheat and rye products is explained. At the end of the report an illustrative case is reported. In the treatment of rectal constipation, a diet high in bulk-producing foods including fruits, vege-

tables, coarse breads, cereals, water and foods which ferment slightly are recommended. For those cases of functional diarrhea of course, low-residue nonirritating foods are indicated. In the case of suspected food allergies, elimination diets are necessary for full evaluation.

STANLEY STARK

SEGMENTAL JEJUNAL STENOSIS OF ISCHEMIC ORIGIN: REPORT OF A CASE: Melvin Greenblatt and Harry Goodman. *New England J. Med.* 261:754 (8 Oct.), 1959.

This case report concerns a 47-year old male who was treated for a myocardial infarction without anticoagulants. One week after admission he developed acute epigastric pain followed by repeated emesis three days later. He did well but six weeks after hospital discharge, he was readmitted with severe recurrent epigastric pain. Flat plate revealed a dilated hoop-shaped loop of small bowel. One week later symptoms recurred and a gastrointestinal series revealed a dilated segment of jejunum which narrowed

abruptly with a 7 cm. stenotic area. At operation, this same area was found 46 cm. distal to the ligament of Treitz. The segment was resected with uneventful recovery. Pathologically an organized thrombus of the mesenteric artery was found. It is noted that besides symptoms of stricture, other cases have been reported which showed symptoms of malabsorption states or intestinal angina.

STANLEY STARK

ULCERATIVE PROCTOCOLITIS: Frederick B. Campbell, Joe E. Hirsch and John G. Campbell. *Missouri Med.* 56:1137 (Oct.), 1959.

A brief review of nonspecific ulcerative colitis is given with emphasis on the nature, duration, etiology and complications of this illness.

Many times the first exposure of the pa-

tient to a physician is to the proctologist because of localized rectal symptoms. Sig-moidoscopic examination is the easiest method of diagnosis when proctitis alone is present and when clinically the symptoms

are those of urgency with the passage of mucus.

In the authors' experience, 75 per cent of these patients respond to medical therapy with a routine of diet, antispasmodics, sedatives, and the rectal instillation of Nisulfazole (10 per cent suspension) with hydrocortisone after each stool.

When proctocolitis occurs, symptoms may be mild to severe with the indications for colectomy being listed. These are: 1. impending or suspected perforation indicated by fever, toxicity, distention, and tenderness from peritoneal irritation of peri-

colitis; 2. massive hemorrhage; 3. deep perirectal fistula formation; 4. systemic manifestations—arthritis, dermatitis, iritis, myocarditis, *erythema nodosa*; 5. chronic invalidism and interference with earning a livelihood or comfortable living; 6. partial obstruction, and 7. suspected carcinomatous change.

Practical comments are made as to the preferred surgical type of ileostomy and the management of the ileal stoma and the surrounding skin.

MORTON SCHWARTZ

A FORM FOR RECORDING SIGMOIDOSCOPIC EXAMINATIONS OF DYSENTERY CASES: Marion M. Brooke, Richard Mason and Albert V. Hardy. U. S. Armed Forces M. J. 10:1174 (Oct.), 1959.

During the study of dysentery among the prisoners of war on Kojima Island in Korea, the authors had performed from 30 to 100 or more sigmoidoscopic examinations daily. Under such conditions it was too time consuming to record the observations by handwritten narratives. Furthermore, since the therapeutic effects of various drugs were being evaluated, it was important to have the observations as standardized and as objective as possible. This was particularly pertinent inasmuch as during the seven months of the investigation it was necessary for several persons to perform the examinations. As a consequence, a form was devel-

oped to facilitate the recording of objective observations and to make possible more accurate comparisons between sigmoidoscopic examinations.

This reporting form is described in detail which was used to record the results of the sigmoidoscopic examinations of over 2,000 dysentery cases during an epidemic in Korea, and proved to be of great assistance in the diagnosis of new cases and in assessing the response to therapy. Persons interested in trying the form may obtain copies from any of the authors.

ALVIN D. YASUNA

OMENTAL LYMPHANGIOMA: John L. Savage. Quart. Bull. Northwestern M. School 33:262 (Fall), 1959.

This is an additional case of a cystic omental lymphangioma preoperatively diagnosed as an appendiceal perforation.

While only 120 cases have been described in the literature the authors feel the incidence must be higher.

The possibility should be considered in acutely distended abdomens of children when a large mass is present. Prognosis is good after surgical removal.

A. M. SUSINNO

TREATMENT OF BEEF TAPEWORM INFESTATION: Robert Lussky. Quart. Bull. Northwestern Univ. M. School 33:240 (Fall), 1959.

Two patients resistant to quinacrine therapy for beef tapeworm infestation were successfully treated by a modified De Rivas transabdominal intubation method.

The effective use of solutions of magnesium sulfate, glycerine and warm saline has been described by various investigators since the original De Rivas report in 1932.

However, the results in the two patients

treated by the authors appear to show that this method is quite free of discomfort even for the younger patients.

With other forms of therapy children more often experience toxic manifestations but the 10-year old female treated by the authors became immediately symptom-free without distressful events due to therapy.

A. M. SUSINNO

ILEOCECAL HEMORRHAGE: Duncan Shepard. J. M. A. Georgia 48:503 (Oct.), 1959.

There is still controversy over the anatomy of the ileocecal valve due to variations in the normal valve and the difference between its appearance during life and in the cadaver. No agreement exists about whether an ileocecal sphincter exists or whether competency of the valve is due to the two lips being pushed together by intracecal pressure.

Furthermore, there is no typical clinical picture of prolapse of the ileocecal valve, lipoma, or lipomatous infiltration of the valve.

The benign and malignant lesions inherent to the colon are found in the ileocecal

valve as well as inflammatory changes whose etiology is difficult to determine. Edema of the valve may be idiopathic or secondary to prolapse of the ileal mucosa or to intermittent relenting intussusception.

Three cases of prolapse of the ileal mucosa through the ileocecal valve are reported. One of these was associated with lipomatous infiltration of the ileocecal valve. All of them were accompanied by exsanguinating melena and two of the cases had preceding attacks of mild, crampy, lower abdominal pain. This lesion must be considered as a possible cause for melena.

ALVIN D. YASUNA

LIVER AND BILIARY TRACT**JAUNDICE IN EARLY INFANCY: M. A. Kibel. Central Afr. J. Med. 5:468 (Sept.), 1959.**

It is noted that about one-half of all newborn infants show some degree of jaundice during the first two weeks of life. Many of these cases of so-called physiological jaundice are actually due to other causes. An important point is stressed that when 20 mg. per 100 c.c. of bilirubin is present in the blood, kernicterus may result. This will occur at lower levels in premature infants. Emphasis is placed on the rapidity at which these extreme levels can be attained when a pathological condition exists.

Brief but excellent discussion is made about physiological jaundice in full-term infants, premature infants, and the prolonged type of "physiological jaundice". Under the discussion of hemolytic disease of the newborn—a most practical chart is

available as to the differentiation of jaundice of Rh incompatibility and ABO incompatibility.

Other less frequent causes of jaundice are stressed—particularly those of an infective etiology. Septicemia is the most important of these and should be first thought of when a jaundiced infant is ill; with the organism generally being a staphylococcus, streptococcus, or *E. coli*.

Other more rare causes of jaundice in early infancy are briefly discussed.

It should be reemphasized that icterus in the first 24 hours is abnormal and that not all children showing jaundice after 24 hours have "physiological jaundice".

MORTON SCHWARTZ

ROENTGENOGRAPHIC AIDS IN DIAGNOSIS OF NEOPLASMS OF LIVER AND EXTRAHEPATIC DUCTS: John A. Evans and Zuheir Mujahed. J.A.M.A. 171:7 (5 Sept.), 1959.

The authors reviewed the roentgenographic examination of 35 patients with primary carcinoma of the gallbladder. Fourteen (40 per cent) showed some detectable abnormality on one or more x-ray studies. About ⅔ of those patients who had a gastrointestinal series showed evidence of extrinsic pressure on the first or second portion of the duodenum. Other roentgenographic examinations showed the presence of a mass in the right upper quadrant on plain film of

abdomen, displacement of hepatic flexure on barium enema in 1 out of 26 cases and displaced right kidney in 1 out of 19 in I. V. Pyelography studies, opacification of the biliary system was found in 4 out of 26 cases on oral cholecystography.

The diagnosis of a polypoid growth was made by the finding of a smooth fixed non-calcified filling defect, less than .5 mm. and never greater than 1 mm. in size. This, because of the possibility of malignant poten-

tiality, calls for cholecystectomy.

Cholangiography at operation or in the postoperative period is of little help in the diagnosis of bile duct neoplasm. A filling defect due to malignancy cannot be differentiated from calculous disease. I V. cholangiography has not been helpful.

Other technics such as percutaneous

transhepatic cholangiography, though risky, has been helpful in the presence of clinical or chemical jaundice. Percutaneous splenoportal venography provides excellent visualization of the portal vein and its intrahepatic components, particularly the right lobe of the liver.

SAUL A. SCHWARTZ

WATER-BORNE INFECTIOUS HEPATITIS: James W. Mosley. *New Engl. J. Med.* 261:748 (8 Oct.), 1959.

Water-borne epidemics of infectious hepatitis have occurred in towns of over 3,000 population down to areas with small private supplies. The peak month is usually August with some cases seen throughout the winter months. Incubation period in one epidemic ranged from 26 to 38 days. The shorter the span of the epidemic and the larger the number of cases, the more likely it is that some common carrier such as water is the cause. The attack rates have varied from 12 to 40 per cent. The age distribution seems

to be in an older age group than that seen in endemic hepatitis which primarily strikes children. Adult groups living in poorer housing seemed to have a lower attack rate than the wealthier. Apparently fairly high amounts of chlorine are necessary to inactivate the virus in water. It is surprising in view of the resistance of the virus and the frequent fecal contamination of water supplies, that water-borne epidemics are not more prevalent.

STANLEY STARK

RECENT ADVANCES IN ROENTGENOLOGY OF THE BILIARY SYSTEM: Lester W. Paul. *Missouri Med.* 56:1123 (Oct.), 1959.

The author discusses the different types of iodine preparations used in roentgenology of the biliary system and the relative advantages of these media.

Of these media, iopanoic acid (Telepaque) is apparently the most widely used, and about which most of this discussion revolves.

If the gallbladder has been removed or if the cystic duct is occluded, it often is possible to opacify the common bile duct by increasing the dose of Telepaque to 2 or 3 times the usual amount (6 to 9 gm.).

The author often uses this method of oral cholangiography and many times has been able to visualize the common duct this way.

A review of the use of intravenous cholangiography with the preparation of Cholografin is made with the advantages and shortcomings of this procedure.

The author's comments on recent interesting observations by Salzman and coworkers

regarding opacification of nonopaque stones are worthy of mention. They found that when Telepaque was given for a period of four days in daily doses of 3 gm. (1 gm. three times daily), roentgenograms taken on the fifth day demonstrated opacification of the periphery of stones within the common duct or gallbladder which were previously not visible. Apparently the continued bathing of the stone in the contrast-containing bile leads to an interaction of bile pigments on the surface of the stone and the contrast material so that a ring contoured shadow of the stone develops. They were able to show stones in the duct even in the presence of jaundice and feel that this procedure, which they call the "four-day Telepaque test" is probably the best method available for demonstrating common bile duct stones in the jaundiced patient.

MORTON SCHWARTZ

FATAL JAUNDICE AFTER ADMINISTRATION OF BETA-PHENYLISOPROPYL-HYDRAZINE: D. T. Beer and Fenton Schaffner. *J.A.M.A.* 171:887 (17 Oct.), 1959.

A fatal case of jaundice was reported in a 65-year old female after intake of 600

mg. of beta-phenylisopropylhydrazine (Catron) over a period of 6 weeks. The dosage

used was 18 mg. a day for two weeks and a maintenance dose of 12 mg. daily in conjunction with chlorothiazide and reserpine.

Her blood pressure of 240/120, which was unresponsive to chlorothiazide, hydralazine, ganglionic blocking agents and reserpine was reduced to 160/90 after two weeks of beta-phenylisopropylhydrazine therapy. The patient failed to report the occurrence of jaundice and continued her medication for one week prior to admission.

The clinical, laboratory and pathological findings in the liver were identical to those in jaundice caused by iproniazid, which is an analogue of beta-phenylisopropylhydrazine, and were indistinguishable from severe viral hepatitis.

The drug is a congener of amphetamine and is a hydrazine derivative with dual

functions of monoamine oxidase inhibitor and dihydroxyphenylamine (DOPA)-decarboxylase coenzyme inhibition. It has been used with success in treatment of mental depression, angina pectoris, rheumatoid arthritis and experimentally in hypertension. In the latter disorder, excellent results have been attained without toxicity, in reported cases with doses varying from 6.25 to 25 mg. per day for at least 2 months.

None of the currently available hepatic tests seem to be of value in predicting the appearance of jaundice but alteration of the results of any of them, particularly serum bilirubin or transaminase during therapy should be followed by immediate cessation of the use of the drug.

JOSEPH E. WALTHER

STUDY OF THREE HUNDRED EIGHT OPERATIONS FOR STRICTURE OF BILE DUCTS: Waltman Walters and J. A. Ramsdell. J.A.M.A. 171:782 (17 Oct.), 1959.

The results of 308 operations in 265 patients who had surgery for stricture of bile ducts were analyzed. The time interval from the date of operation and time of the study was from one to 25 years. In every case but one the stricture followed surgical injury. The procedures performed to correct the strictures were usually either choledochocholedochostomy or choledochoduodenostomy. The results following the two types of operations were approximately the same, with 68 and 69 per cent of good or excellent results occurring. Among the 191 patients followed for more than 5 years,

there were 28 deaths and 16 of these were from cirrhosis or liver failure. Cirrhosis of the liver is not a contraindication to surgery unless ascites is present, although it increases the risk because of the collateral circulation and the prognosis is less favorable.

T-tubes were left in for 6 to 9 months and the Mayo-Sullivan tube from weeks to months. The proper length of time for the prosthetic splint to remain in the anastomosis to prevent constriction is still being investigated.

JOSEPH E. WALTHER

INFECTIOUS HEPATITIS: DETECTION OF VIRUS DURING THE INCUBATION PERIOD AND IN CLINICALLY INAPPARENT INFECTION: Saul Krugman, Robert Ward, Joan P. Giles, Oscar Bodansky and A. Milton Jacobs. New Engl. J. Med. 261:729 (8 Oct.), 1959.

Attempts were made during the course of a severe outbreak of infectious hepatitis at a state school to isolate the virus during the incubation period, the early icteric phase, in clinically inapparent infection, and two to three weeks after the onset of jaundice. Both stool and blood studies were performed. The usual criteria were used for detection of the disease with or without jaundice. The results revealed that virus was detected in stools and blood during the incubation period and early in the course of the disease. Stools were infective on the 25th day of the incubation period (2 or 3

weeks before onset of the jaundice) and one to eight days after onset of the jaundice. Viremia was detected on the 25th day of the incubation period; three to seven days before jaundice and on the third day of jaundice. Abnormal serum transaminase activity appeared to be the most sensitive indicator of infection and it is recommended that this test be performed on all blood donors as a screening test although it is not perfect since it is usually still normal on the 25th day of the incubation period when the donors are already infective.

STANLEY STARK

FATTY INFILTRATION IN THE LIVER—RESPONSE TO TREATMENT: Charles H. Brown and Mauro Merlo. *Cleveland Clin. Quart.* 26:153 (Oct.), 1959.

This is an excellent clinical report. It illustrates the maxim that biological reactions are reversible or irreversible and that in this instance most of the changes are of the reversible type. The fibrosis which has occurred prior to the institution of therapy persists. The treatment consists of the avoidance of alcohol, a high protein, high calorie diet, supplemented by Vitamin B

preparation and lipotropic agents. The results of therapy were evaluated clinically, biochemically and histopathologically (Needle biopsies) Fatty infiltration of the liver may produce all the signs and symptoms of liver failure including jaundice and ascites.

IRVIN DEUTSCH

PRIMARY INTRAHEPATIC CHOLESTASIS DUE TO HODGKIN'S DISEASE WITH RESPONSE TO ADRENOCORTICOTROPIN. Bruce L. Brown. *Ohio Med. J.* 55:1384 (Oct.), 1959.

Liver involvement in Hodgkin's disease may occur as frequently as in 58 per cent of cases, but no reports of the types of jaundice could be found in the literature by the author, although it is stated to occur in 10 per cent of the patients with hepatomegaly. The author reports a case of proved Hodgkin's disease in a 22-year old white male who developed jaundice six years after a positive cervical gland biopsy. The laboratory studies revealed a markedly elevated serum bilirubin and alkaline phosphatase with a normal thymol turbidity reading. Because of the possibility of cholangiolitic hepatitis unrelated to Hodgkin's disease, ACTH Gel was given 40 mg. intra-

muscularly daily. The serum bilirubin fell to 2.8 mg. in 3 days, a response characteristic of cholangiolitic hepatitis as distinguished from extrahepatic obstruction. However, exploratory laparotomy and liver biopsy confirmed the diagnosis of Hodgkin's cellular infiltrates forming tumor-like nodules. The author concludes that this case demonstrates the lack of specificity of adrenocorticotropin for cholangiolitic hepatitis and lends further support to the concept of Chalmers that adrenocorticotropin may bring about a change in the usual pathways of bilirubin metabolism.

SAMUEL M. GILBERT

ACUTE LESIONS OF THE BILIARY TRACT: Warren H. Cole. *Illinois Med. J.* 116:213 (Oct.), 1959.

The author discusses two acute lesions of the biliary tract: 1. *Acute cholecystitis*:—The chief question is when to operate. He is willing to operate within 48 hours of the onset of symptoms if the diagnosis is certain. Only a small proportion of patients reach the hospital at this stage. Actually there is no way of determining which patient will recover by conservative therapy, to have a cholecystectomy later. If the patient is being treated conservatively, he must be watched for signs indicating perforation, when immediate emergency surgery may be indicated. These signs include pain, fever, and muscle spasm. If these signs are present at the time of admission, and fail to subside within 24 to 36 hours, the patient should be operated on, either by cholecystostomy or cholecystectomy. If the patient is quite ill and the gallbladder

embedded deeply in adhesions, it is probably safer to perform a cholecystostomy. With respect to conservative or immediate surgery policy, Cole says that after years of study, he has come to the conclusion that one method is about as good as the other.

2. *Acute suppurative cholangitis*:—This lesion is caused by obstruction of the common duct, usually a stone, occasionally carcinoma of the pancreas or ampulla of Vater. The object of treatment is to prevent serious liver damage, including multiple abscesses. If the patient is extremely ill with chills, fever and high pulse rate, operative mortality is high; intensive therapy with antibiotics is instituted, and if the patient's condition improves but temperature does not subside within two or three days, surgery is indicated. If the patient is in comparatively good condition but has high

fever, chemotherapy for one or two days may be tried, but if complete response is not obtained in a day or two, operation should be carried out. Surgery consists of

removing the stones and draining the common duct.

SAMUEL L. IMMERMAN

ECHINOCOCCOSIS: T. W. Dorman and E. S. Olson. Wisconsin Med. J. 58:603 (Oct.), 1959.

Echinococcosis is seen most often in sheep and cattle-raising areas. The *echinococcus granulosus* is the smallest tapeworm of medical importance. It ranges from 2.5 cm. to 9 mm. It lives in the lower duodenum and upper jejunum. It has a scolex, neck, and three segments. The intestines contain thousands of the worm. The ova contaminate grass and vegetables; the fur of diseased animals is also infected. The ova from the feces is ingested by man or other intermediary hosts. The embryo enters the lymphatics or venules and is carried to the liver, lungs or other organs where it develops into a hydatid cyst.

There are three types of hydatid cysts seen in man:

1. Unilocular—is most common, grows slowly and requires several years for development. They vary in size and may reach 15-20 cm. in diameter.

2. Osseous cysts—grow along the bony canals with erosion and invasion into the medullary cavities. Spontaneous fracture is common.

3. Alveolar cysts—grow similar to a neoplastic tumor. They are not well circumscribed and invade the surrounding tissues. They give rise to metastasis in other organs. Symptoms depend on location and are those of a slowly growing tumor. Symptoms are acquired in childhood but develop later in life. Prognosis is good if tumor is accessible to surgery.

Diagnosis is made by skin tests, complement-fixation tests, and the Bentonite flocculation test may be helpful. This is still in the experimental stage. The antigen consists of sterile hydatid fluid extracted from the polysaccharide portion of the hydatid solids.

Treatment is surgical. Exteriorize the cyst and ten days later inject 40 per cent formalin or absolute alcohol which kills the cyst. A calcified cyst should be left alone. Chemotherapy is ineffective. Preventative measures should be instituted to prevent the dog from being contaminated.

LOUIS K. MORGANSTEIN

CONGENITAL ABSENCE OF THE GALLBLADDER: A STATISTICAL STUDY: Stanley Edwin Monroe. J. Int. Coll. Surg. 32:369 (Oct.), 1959.

Congenital absence of the gallbladder is a rare occurrence, 1:7500 cases. It is divided equally between the two sexes. It may be the cause of nonvisualization of the gallbladder. In about 3% of the cases this anomaly was associated with one or more other congenital defects, such as atresia of the hepatic or common duct, absence of common bile duct, cystic dilatation of common bile duct and choledocholithiasis.

In fibrocystic disease congenital anomaly

lies of the extrahepatic biliary system is frequent. Abnormalities observed elsewhere were numerous and extremely varied. The author then enumerates in great detail the various and numerous congenital defects and anomalies that were found in the cardiovascular system, gastrointestinal system, genitourinary system, central nervous and skeletal systems, etc.

LOUIS K. MORGANSTEIN

EXCRETION OF DEMETHYLCHLORTETRACYCLINE INTO THE BILE: Calvin M. Kunin and Maxwell Finland. New Engl. J. Med. 261:1069 (19 Nov.), 1959.

Concentrations of demethylchlortetracycline in simultaneously obtained samples of serum and bile were determined at intervals after a single intravenous injection of 500 mg. of this antibiotic, dissolved in 150

ml. of 5 per cent dextrose solution, in four women who had T-tubes in the bile ducts after cholecystectomy. Demethylchlortetracycline, like the three earlier analogues, chlortetracycline, oxytetracycline, and tetra-

cycline, is concentrated in the liver and excreted in the bile at levels up to more than 30 times greater than those found simultaneously in the serum. It may be concluded that the higher and better sustained

levels of the antibiotics are the result not of diminished biliary excretion but primarily of its greater stability and slower rate of renal excretion.

ERNEST LEHMAN

SPLEEN

ROENTGEN FINDINGS IN SPLENIC HEMORRHAGE: John R. Amberg, Julio P. O'Leary. Wisconsin M. J. 59:363 (June), 1960.

Incidence of splenic rupture is 20 to 36 per cent in closed abdominal trauma.

The clinical picture may be quite characteristic with evidence of external trauma, signs of shock and upper abdomen quadrant spasm. There are two situations of diagnosis, in which the diagnosis of splenic rupture is extremely difficult. 1. When hemorrhage is slow. 2. When the hemorrhage is delayed.

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with alteration contour of the stomach and colon. 3. Blood accumulation in the left gutter with haziness in the left flank. The left colon, may be displaced medially, and peritoneal fat line straightened. 4. If blood diffuses throughout the abdomen, with the loops of small bowel separated by diffuse cloudiness as well as bulging of the flanks.

Treatment consists of early splenectomy. Of the 25 cases presented, the mortality rate was 36 per cent of the entire group; those undergoing splenectomy 20 per cent.

V. J. GALANTE

ULCERS HEALED

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References:

1. Damrau, F., *Am. J. Gastroenterol.* 35:612, 1961.
2. Hamilton, R.R., *Brit. M.J.* 2:827, 1955.
3. Feinblatt, H.M., *Journal-Lancet.* 80:37, 1960.
4. Kupersmith, I.H., *Am. J. Gastroenterol.* 28:439, 1957.

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

CIBA FOUNDATION TENTH ANNIVERSARY SYMPOSIUM: SIGNIFICANT TRENDS IN MEDICAL RESEARCH: Editors for Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B.; Cecilia M. O'Connor, B.Sc.; Maeve O'Connor, M.B., M.R.C.P., 356 pages, 41 illustrations, Little, Brown and Company, Boston, Mass., 1959. Price \$9.50.

The Ciba Foundation's 50th volume in the series contains the proceedings of the Tenth Anniversary Symposium.

The combined papers and discussions are representative of the whole broad spectrum

of medical research today.

A name and cross index are of added value to this interesting and instructive book on medical research.

A PRACTICAL GUIDE FOR SURGICAL MANAGEMENT: Julian A. Sterling, M.D., Sc.D., F.A.C.G., F.A.C.S., F.A.A.S. and F.I.C.S., Assistant Professor of Surgery, Graduate School of Medicine, University of Pennsylvania; Senior Attending Surgeon, Albert Einstein Medical Center; Chief Surgeon, Psychiatric Hospital, Philadelphia with a foreword by Herbert R. Hawthorne, M.D., 67 pages, Vantage Press, New York, 1959. Price \$3.00.

Dr. Sterling has written a veritable guide for the intern, resident and surgeon. It is clear and concise and should be of great value in taking care of surgical patients.

On page 55 the reader will find miscellaneous information beginning with the ad-

mission of the patient and the responsibility of the surgical resident.

Although only 67 pages, nonetheless, it is a valuable guide and is highly recommended.

LA MALADIE LITHIASIQUE DES VOIES BILIAIRES LA LITHIASIE VESICULAIRE—Actualites Hepato-Gastro-Enterologiques de L'Hotel-Dieu, 1958: Guy Albot, M.D., and F. Poilleux, M.D., with the collaboration of numerous clinicians—P. Mallet-Guy, M.D.; M. Roux, M.D. and J. Vallire, M.D., 341 pages, illustrated, Masson & Cie, Paris, France, 1959. Price 45 NF.

This is an excellent review dealing with gallbladder and gallstone disease. There are a great many items which are new, and there is an extensive bibliography both American and foreign.

An interesting chapter, page 105, describes migraine and biliary lithiasis. This is rather of interest to the reviewer, because he called attention to this type of headache many years ago. Patients who suffered with periodic headache usually had no recur-

rence after cholecystectomy.

The reviewer would like to suggest that the publishers have the pages cut before submitting the book for review. It is rather a tedious task to cut the pages and a great deal of time is wasted, however, this is only a suggestion with the hope that future paper cover editions will have cut pages.

A separate insert calls attention to several errors in the text which does not detract from the excellent treatise.

CIBA FOUNDATION STUDY GROUP NO. 3: CANCER OF THE CERVIX—DIAGNOSIS OF EARLY FORMS: In honor of Prof. Dr. C. Kaufmann. Editors for Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P. and Maeve O'Connor, B.A., 114 pages, 27 illustrations, Little, Brown and Company, Boston, Mass., 1959. Price \$2.50.

The symposium on cancer of the cervix by the participants gives a comprehensive view of the diagnostic procedures involved in diagnosis of this frequently overlooked

condition.

An important chapter by Drs. Kaufmann and Ober, page 61, calls attention to the morphological changes of the cervix with

age, and their significance in the early diagnosis of carcinoma. This chapter should be read carefully; the illustrations and discus-

sions by the group are illuminating.

Reference and a short index complete the text.

STUDIE VAN DE LEVERINSUFFICIENTIE PRECOMA EN COMA: Dr. Jan De Groote, 243 pages, Arscia Uitgraven N. V., Brussels, Belgium, 1959.

A comprehensive study dealing with liver insufficiency, precoma and coma. The role of other conditions than ammonia-causing

coma is ably discussed. Here, too, the reviewer suggests translating this valuable study into several languages.

THE LIFESPAN OF ANIMALS: G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P. and Maeve O'Connor, B.A., 324 pages, 58 illustrations, cumulative indexes to volumes 1-5 and author index, Little, Brown and Company, Boston, Mass., 1959. Price \$9.50.

This is the 5th volume by the Ciba Foundation Colloquia on Aging. Although the contents deal with the lifespan of ani-

mals and fishes, it makes interesting reading.

BIOCHEMISTRY OF HUMAN GENETICS: G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P. and Cecilia M. O'Connor, B.Sc., Ciba Foundation Symposium, 347 pages, 60 illustrations, Little, Brown and Company, Boston, Mass., 1959. Price \$9.50.

A valuable addition to medical literature, especially for the hematologist and biochemist. Twenty-nine participants from all parts of the world, including nine American

scientists, have contributed to Biochemistry of Human Genetics. Reference names and cross index, complete the symposium.

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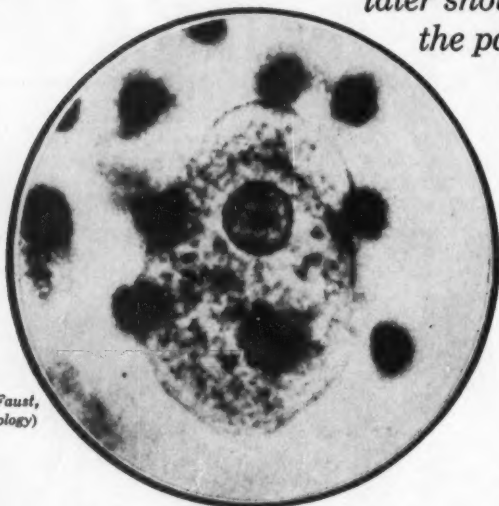
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1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic *Endamoeba histolytica* Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). *Am. J. Gastroenterol.* **34**:429-432 (Oct.), 1960.



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1. Hock, C. W.: Am. J. Gastroenterol. 34:293 (Sept.) 1960.

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Bevilacqua, R. P.: New York J. Med. 59:4573, 1959.

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1. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, *Postgrad. Med.* 26:502-509 (October) 1959.

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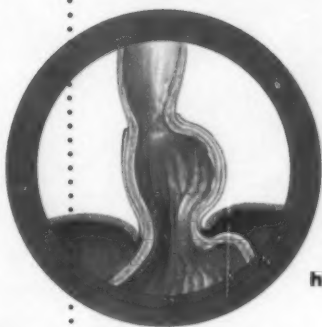
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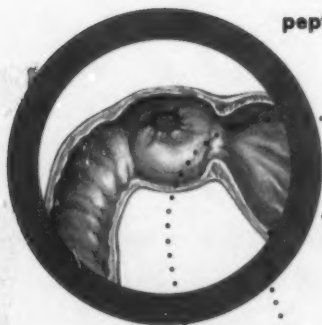
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References: 1. Deutsch, E., and Christian, H.J.: *J. Am. Med. Assoc.* 169:102 (April 25) 1959. 2. Jankelson, I.R., and Jankelson, O.M.: *Am. J. Gastroenterol.* 32:636 (Nov.) 1959. 3. Moffitt, R.E.: *Rhode Island Med. J.* 44:151 (March) 1961. 4. Hollander, E.: *Am. J. Gastroenterol.* 34:613 (Dec.) 1960. 5. Jankelson, O.M., and Jankelson, I.R.: *Am. J. Gastroenterol.* 32:719 (Dec.) 1959. 6. Schwartz, I.R., and Spertus, L.: Scientific Exhibit, A.A.G.P., Miami Beach, April 16-20, 1961.

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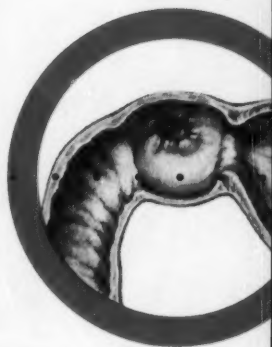
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References: (1) Cohn, E. M.: *Am. J. Gastroenterol.* 35:115 (Feb.) 1961. (2) Jones, M. D.; Sakai, H.; and Rogerson, A. G.: *J. Pediat.* 53:172 (Aug.) 1958. (3) Machella, T. E.: *Gastroenterology* 34:1050 (June) 1958. (4) Orloff, T. L.: *Ann. J. Roentgenol.* 30:618 (Oct.) 1958. (5) Johnson, G., Jr.; Pearce, C.; and Glenn, F.: *Ann. Surg.* 152:91 (July) 1960. (6) McClenahan, J. L.: *Pennsylvania M. J.* 62:188 (Feb.) 1959.

"CHOLOGRAFIN"® AND "DUOGRAFIN"® ARE SQUIBB TRADEMARKS.



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*Squibb Quality —
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For the irritable G.I. tract

Milpath acts quickly to suppress hypermotility,
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MILPATH-400—Yellow, scored tablets of 400 mg. Miltown
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Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

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Now for the first time, your pa-
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because "RIOPAN" is a swallow
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"RIOPAN" is an entirely new chem-
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properties—magnesium and alu-
minum hydroxides—are united in
a single molecule by a patented
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This chemical union makes pos-
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that acts within seconds, provid-
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almost immediately.

A NEW ADVANCE IN LIQUIDS, TOO... "RIOPAN" SUSPENSION

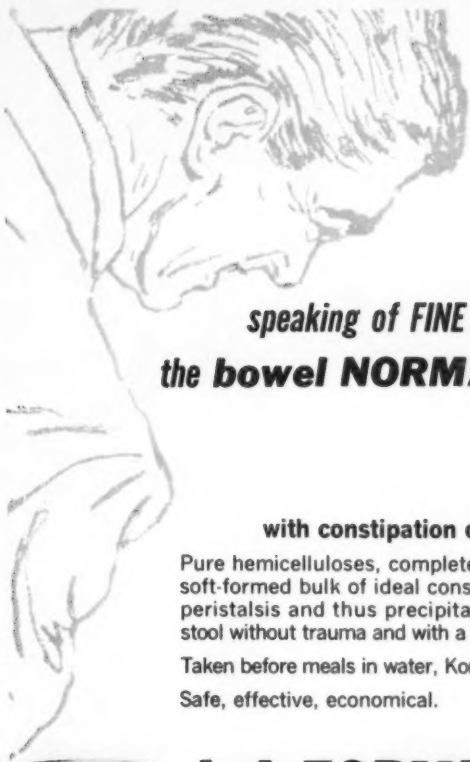
"RIOPAN" Suspension offers a wel-
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cool, clean mint flavor with no
aftertaste—and predictable buf-
fering action, almost immediately
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pH range in both large and small
amounts of HCl, even with vary-
ing dosage.

Dosage: 1 or 2 tablets swallowed
with water as required, or 1 or 2 tea-
spoonfuls of suspension with water
as required; preferably between
meals and at bedtime.

NOTE: In peptic ulcer, and whenever
continuous control of acidity is de-
sired, many clinicians prefer to give
antacid medication at hourly inter-
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Supplied: "RIOPAN" Tablets, No. 790
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ium hydrate (hydrated magnesium
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**for the obese patient
with constipation or non-specific diarrhea**

Pure hemicelluloses, completely calorie-free, producing a soft-formed bulk of ideal consistency to stimulate normal peristalsis and thus precipitate easy passage of a bland stool without trauma and with a minimum of peri-anal soiling.

Taken before meals in water, Konsyl helps to depress appetite.

Safe, effective, economical.



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**for the thin, finicky patient
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Pure hemicelluloses, ultra-pulverized to unique particle size and simultaneously dispersed in highest-grade lactose and dextrose to insure unsurpassed palatability, likewise acting to precipitate easy passage of soft formed stools for maximum relief of abnormal bowel function.

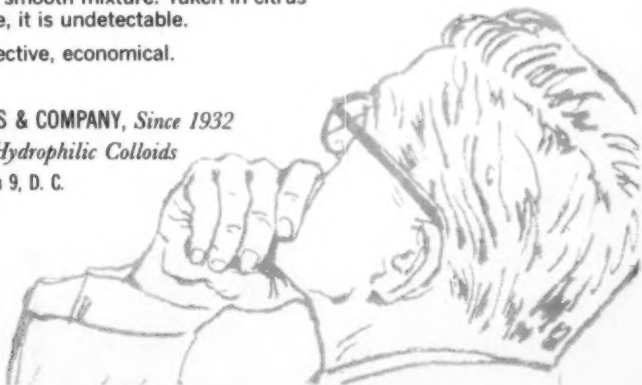
Taken in water or milk, L. A. Formula makes a velvety smooth mixture. Taken in citrus fruit juice, it is undetectable.

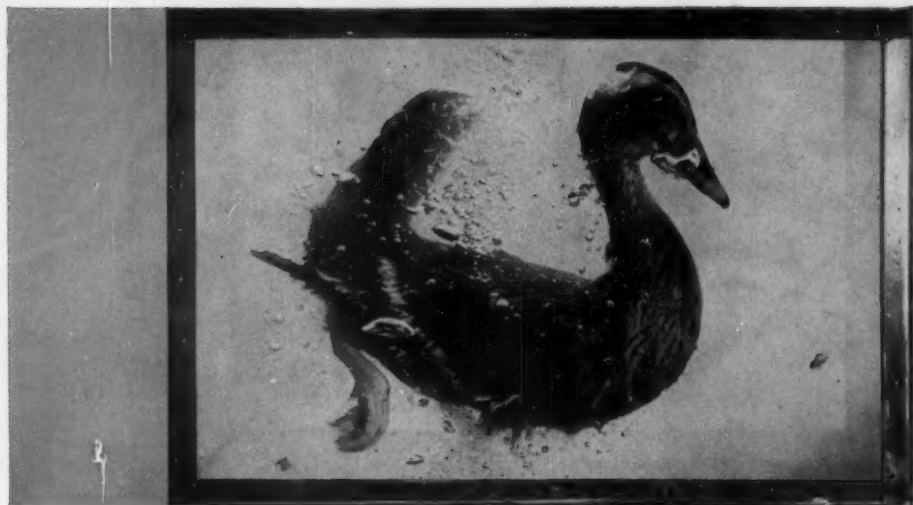
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The principle that makes
a duck sink... produces
soft, normal stools
in functional constipation



Water doesn't roll off this duck's back... because the water is Surfak-treated. Surfak decreases interfacial tension between water and oil... penetrates the natural oils in the feathers, permits water absorption, adding weight so that the duck sinks.

Similarly, in functional constipation, Surfak quickly permeates the heterogeneous fecal mass. The superior surfactant action of calcium bis-(dioctyl sulfosuccinate) reduces the interfacial tension between the aqueous and lipid phases of the intestinal content to minimal values. The result is soft homogeneous feces which are easily moved to evacuation, naturally.

Adults: One 240 mg. Surfak capsule daily.

Children (and adults with minimal needs): One to three 50 mg. Surfak capsules daily.

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